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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 212 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds*. Pergamon Press, London (1956).

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NEIGHBORING METHOXYL PARTICIPATION IN SOLVOLYTIC NUCLEOPHILIC SUBSTITUTION*†‡§

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(*Received* 12 *December* 1957)

Abstract—In the present paper are summarized some of the results of the investigation of MeO-3,4,5,6 and 7 participation in solvolytic substitution. Among the ω-methoxy-l-alkyl bromobenzenesulfonates, solvolysis of the 4-methoxy-l-butyl and 5-methoxy-l-pentyl esters is rapid and dominated by anchimerically assisted ionization in the common solvents. While MeO-5 and 6 participation is important, MeO-3,4 and 7 is not, the corresponding esters solvolyzing with a rate constant essentially equal to the k_s value estimated from a $\rho^*\nu^*$ correlation of solvolysis rates for primary bromobenzenesulfonates solvolyzing without anchimeric assistance. On the basis of the calculated k_s values, ratios of anchimerically assisted and unassisted solvolysis rates ($k\Delta/k_s$) are derived for the MeO-5 and 6 cases.

In the case of MeO-5-assisted ionization of 4-methoxy-1-butyl bromobenzenesulfonate in acetic acid at 25°, an α- or a δ-methyl group is rate-enhancing by a factor of 6. Both the 5-methoxy-2-pentyl and 4-methoxy-1-pentyl esters give rise to an identical mixture of 5-methoxy-2-pentyl and 4-methoxy-1-pentyl acetates from methylene-O cleavage of the common cyclic oxonium ion intermediate.

The participating methoxyl group may be an *o*-methoxyl substituent in a phenyl group, as in *o*-methoxyneophyl, 3-*o*-anisyl-1-propyl, 3-methyl-3-*o*-anisyl-1-butyl and *trans*-2-*o*-anisyl*cyclo*pentyl arenesulfonates. With the compounds investigated, *o*-MeO-5, *o*-MeO-6, but not *o*-MeO-7 participation has proved to be important. Me-O cleavage of the intermediate oxonium ions formed by *o*-MeO-5 and 6 participation is important, so that benzodihydrofurans or benzodihydropyrans are produced, sometimes as the major product.

The behavior of the cyclic oxonium ion intermediates as ion pairs determines some interesting kinetic features of the acetolysis of the methoxyl-substituted alkyl arenesulfonates solvolyzing with methoxyl participation.

BECAUSE of recent interest in δ-methoxyl participation in nucleophilic substitution,[3,4,5] we are prompted to summarize some of the results of our investigation of MeO-3,4,5 and 6 participation in solvolytic substitution.¶

As in other cases of neighboring group participation in nucleophilic substitution, it is helpful to discuss methoxyl participation with the aid of: (i) k_Δ, the rate constant

* Some of the material of this manuscript has been presented[1,2] previously in outline form: S. Winstein, "Neighboring Groups in Substitution and Rearrangement," at Symposium on "Dynamic Stereochemistry," Manchester, England, March 31 1954.

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‡ Supported in part by the Office of Naval Research.
§ Research supported by the Eli Lilly Company.

¶ The symbolism MeO-*n* is employed, where *n* is the size of the ring created in the transition state for the ionization. Analogous symbols have been employed for aryl[6–9] and complex neighboring group participations.

[1] *Chem. & Ind. (Rev.)* 562–563, 569–571 (1954).
[2] S. Winstein, *Experientia Supplementum* II, 137 (1955).
[3] D. S. Noyce and B. R. Thomas, *J. Amer. Chem. Soc.* **79**, 755 (1957).
[4] S. Oae, *J. Amer. Chem. Soc.* **78**, 4032 (1956).
[5] A. Kirrmann and N. Hamaide, *Bull. Soc. Chim. Fr.* **6**, 789 (1957).
[6] R. Heck and S. Winstein, *J. Amer. Chem. Soc.* **79**, 3105 (1957).
[7] R. Heck and S. Winstein, *J. Amer. Chem. Soc.* **79**, 3114 (1957).
[8] F. L. Scott, R. E. Glick and S. Winstein, *Experientia* **13**, 183 (1957).
[9] L. Goodman and S. Winstein, *J. Amer. Chem. Soc.* **79**, 4788 (1957).

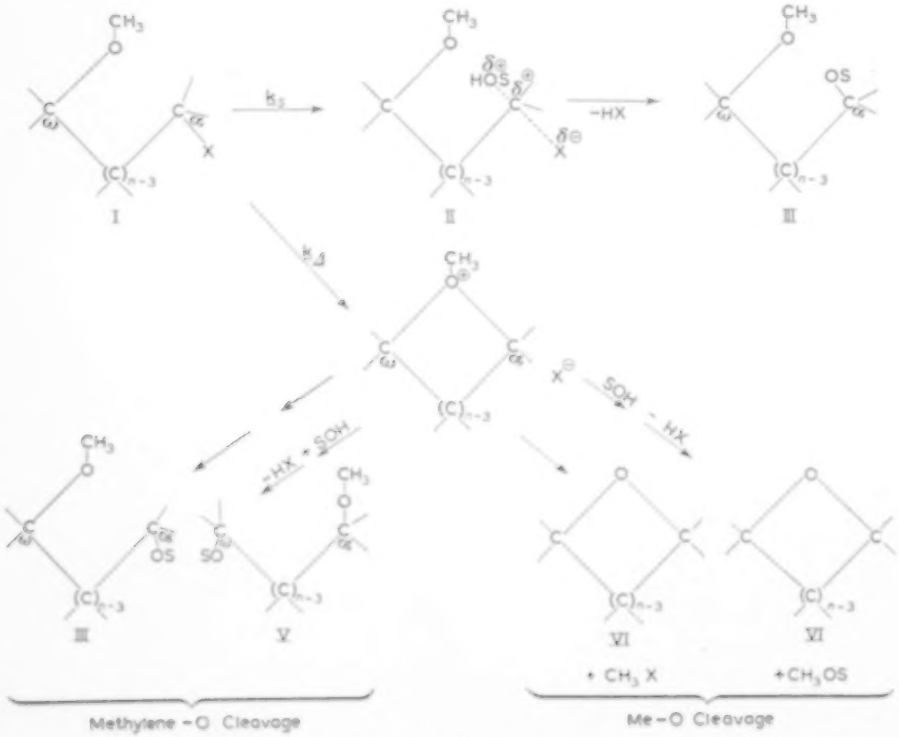
for anchimerically[10] assisted ionization; (ii) k_s, the rate constant for solvolysis not anchimerically assisted, but assisted by whatever nucleophilic solvent participation is appropriate for the substrate structure involved and the solvent being employed;[11] and (iii) k_c, the rate constant for an idealized process involving neither anchimeric assistance nor assistance from nucleophilic solvent participation. On this basis the ratio k_Δ/k_s is a measure of the competition between anchimerically assisted and anchimerically unassisted solvolysis processes. It is sometimes usefully expressed in the form of equation (1), k_Δ/k_c being

$$\frac{k_\Delta}{k_s} = \frac{k_\Delta/k_c}{k_s/k_c} = \frac{k}{k_s} - 1 \qquad (1)$$

a measure of anchimeric assistance and k_s/k_c being a measure of assistance of anchimerically unassisted solvolysis by nucleophilic solvent participation.

ω-Methoxyalkyl Bromobenzenesulfonates

On examining the relative rates of solvolysis of ω-methoxylalkyl bromobenzenesulfonates summarized in Table 1, it is quite evident that solvolysis of the 4-methoxy-1-alkyl and 5-methoxy-1-alkyl bromobenzenesulfonates in the common solvolyzing solvents is rapid and dominated by anchimerically assisted ionization. On the other



[10] S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *J. Amer. Chem. Soc.* **75**, 147 (1953).
[11] S. Winstein, E. Grunwald and H. W. Jones, *J. Amer. Chem. Soc.* **73**, 2700 (1951).

TABLE 1. COMPARISON OF RATES OF SOLVOLYSIS OF ω-METHOXY-1-ALKYL *p*-BROMOBENZENESULFONATES

Compound	AcOH		Relative rates			Calculated k/k_s at 75°		
	$\Delta H\pm$ (kcal/mole)	$\Delta S\pm$ (entropy units)	EtOH 75°	AcOH 25°	HCOOH 75°	EtOH	AcOH	HCOOH
$CH_3(CH_2)_2CH_2OBs$	23·7	−17·4	1·00	1·00	1·00	0·93	0·81	1·07
$CH_3OCH_2CH_2OBs$	23·0	−22·1	0·25	0·28	0·10	1·33	1·51	0·85
$CH_3OCH_2CH_2CH_2OBs$	23·8	−17·9	0·67	0·63	0·33	1·14	1·20	0·84
$CH_3OCH_2(CH_2)_2CH_2OBs$	22·0	−10·4	20·4	657[a] (2200)[b]	461	22·2	425[a] (987)[b]	610
$CH_3OCH_2(CH_2)_3CH_2OBs$	21·6	−15·1	2·84	123	32·6	2·42	47·2	30·6
$CH_3OCH_2(CH_2)_4CH_2OBs$	23·9	−16·5	1·19	1·16	1·13	0·87	0·71	0·85

[a] Based on k_t°.
[b] Based on k_{ext}° from special salt effect of lithium perchlorate.

hand, the rates of solvolysis of the 2-, 3- and 6-methoxy-1-alkyl esters are either lower than or nearly equal to that of the *n*-butyl analog. In fact, these rate constants are essentially equal to the k_s values, which can be estimated from a $\rho^*\sigma^*$ correlation[12,13,14] of solvolysis rates for primary bromobenzenesulfonates solvolyzing without anchimeric assistance.

$\rho^*\sigma^*$ Correlation of k_s values

In Tables 2 and 3 are summarized the application of the $\rho^*\sigma^*$ treatment, which takes account only of the polar effect of the R group of the substrate RCH_2OBs molecules, to data from these Laboratories on a number of systems. In the summarized correlation, R denotes ω-substituted alkyl, the substituent being CH_3O, Cl, Br, I, C_6H_5 and *p*-$CH_3OC_6H_4$. When solvolysis receives a contribution from k_Δ, the correlation is based on the k_s portion of the solvolysis rate constant.

In plots of log *k* for solvolysis of RCH_2OBs vs. σ^*, the point for R = Me consistently falls off the least-squares line defined by the other points.[14] Therefore, it has been omitted from the least-squares line, the data being fit to equation (2). As is clear from Tables 2 and 3, this

$$\log (k_R/k_{CH_3}) = a + \rho^*\sigma^* \qquad (2)$$

treatment fits anchimerically unassisted solvolysis of RCH_2OBs substrates in ethanol, acetic acid and formic acid solvents with a probable error in log (k_R/k_{CH_3}) of ca. 0·05. With the aid of equation (2) and the parameters summarized in Table 3, one can therefore estimate the k_s portion of the solvolysis rate constant for the RCH_2OBs substrates whose solvolysis is being examined for anchimeric assistance.

MeO-5 *and* MeO-6 *participation*

The k/k_s values for solvolysis of RCH_2OBs, based on observed *k* values and k_s values predicted by equation (2), are summarized in Table 1. From these it is evident that k_Δ/k_s is substantial for MeO-5 and MeO-6 participation, but essentially negligible

[12] R. W. Taft, Jr., *J. Amer. Chem. Soc.* **75**, 4231 (1953).
[13] R. W. Taft, Jr. in M. S. Newman, *Steric Effects in Organic Chemistry* Chap. 13. Wiley, New York (1956).
[14] A. Streitwieser, Jr., *J. Amer. Chem. Soc.* **78**, 4935 (1956).

TABLE 2. THE ρ^* σ^* CORRELATION OF SOLVOLYSIS RATES OF SOME PRIMARY BROMOBENZENESULFONATES (RCH_2OBs) AT 75°

R of RCH_2OBs	σ^*	k_R/k_{CH_3} in EtOH		k_R/k_{CH_3} in AcOH		k_R/k_{CH_3} in HCOOH	
		obs.	calc.	obs.	calc.	obs.	calc.
CH_3	0·000						
CH_3CH_2	−0·100[a]	0·5565[f]	0·5311	0·6029[f]	0·6460		
$CH_3(CH_2)_2$	−0·115[a]	0·5213	0·5586	0·5515	0·6760	0·7807	0·7313
CH_3OCH_2	+0·520[a]	0·1315	0·1243			0·0750	0·0878
$CH_3O(CH_2)_2$	+0·140[b]	0·3472	0·3056	0·3596	0·3000	0·2610	0·3123
$CH_3O(CH_2)_3$	−0·218[b]	0·6185	0·7125	0·6691	0·9417	0·8794	1·0034
$ClCH_2$	+1·050[a]	0·0316	0·0355	0·0155[c,g]	0·0164	0·0161	0·0150
$Cl(CH_2)_2$	+0·385[a]	0·2009	0·1711	0·1636	0·1371	0·1318	0·1378
$Cl(CH_2)_3$	+0·063[b]			0·4632[d]	0·5731		
$BrCH_2$	+1·000[a]			0·0156[c,g]	0·0192		
$Br(CH_2)_2$	+0·362[b]			0·1555	0·1476		
$I(CH_2)_2$	+0·293[b]			0·1654	0·1840		
$C_6H_5CH_2$	+0·215[a]	0·2376[c,h]	0·2569	0·3118[i]	0·2361		
$C_6H_5(CH_2)_2$	+0·080[a]	0·4509[f]	0·3521	0·3933[j]	0·3626	0·4364[j]	0·3814
$C_6H_5(CH_2)_3$	+0·020[a]			0·5037[e,j]	0·4403	0·6096[e,j]	0·5326
p-$CH_3OC_6H_4CH_2$	+0·12	0·2564[c,e,g,h]	0·3199				

[a] Values quoted by Taft.[15]
[b] Calculated by using the equation:

$$\sigma^*X(CH_2)_n = -\frac{\sigma^*X(CH_2)_{n-1}}{f} + \sigma^*CH_2(CH_2)_{n-1}$$

with f equal to 2·165, the value given by the σ^* values for $ClCH_2$- and $Cl(CH_2)_2$-.
[c] Rate of toluenesulfonate relative to that of ethyl toluenesulfonate; 100° in case of acetic acid solvent.
[d] Based on $k_{exp.}$ value.
[e] Based on k_s value.
[f] Data of P. Magee.
[g] Data of H. Marshall.
[h] Data of Winstein *et al.*[10]
[i] Data of Winstein and Heck.[16]
[j] Data of Heck and Winstein.[6]
[k] Data of E. Jenny.

TABLE 3. SUMMARY OF LEAST-SQUARES FITS OF SOLVOLYSIS RATES OF PRIMARY ALKYL p-BROMOBENZENESULFONATES BY THE EQUATION LOG $(k_R/k_{CH_3}) = a + \rho^*\sigma^*$

Solvent	n[a]	a	ρ^*	r[b]
EtOH	10	−0·3711	−1·0275	0·044
AcOH	13	−0·3286	−1·3876	0·056
HCOOH	8	−0·3026	−1·4496	0·040

[a] n is the number of pieces of data included in the least-squares line.
[b] Probable error in log (k_R/k_{CH_3}) calculated from the equation

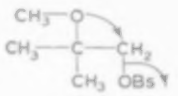
$$r = \pm 0{\cdot}6747\left(\frac{\sum d_i^2}{n-1}\right)^{\frac{1}{2}} \quad (i = 1, \ldots n)$$

where d is the difference between experimental and calculated values.

[15] R. W. Taft, Jr. in M. S. Newman, *Steric Effects in Organic Chemistry* p. 619. Wiley, New York (1956).
[16] S. Winstein and R. Heck, *J. Amer. Chem. Soc.* **78**, 4801 (1956).

for MeO-*n* participation, where *n* is 3, 4 or 7. The sequence of k_Δ values for different ring size *n* of the cyclic oxonium ions (IV) is $3,4 \ll 5 > 6 > 7$, similar to the sequence observed in formation of cyclic immonium ions.[17]

It is clear that the driving force due to neighboring methoxyl participation is very high for $n = 5$ and substantial for $n = 6$. Thus anchimerically assisted ionization dominates solvolysis of $MeO(CH_2)_4OBs$ in ethanol, acetic acid and formic acid, and that of $MeO(CH_2)_5OBs$ in the latter two solvents. For $n = 3$, 4 and 7, the driving force is sufficiently low that anchimerically assisted ionization does not compete with the anchimerically unassisted process in the case of the simple primary RCH_2OBs substrates. It should be noted, however, that k_Δ/k_s depends markedly on structure.[18] For $n = 3$, for example, MeO-assisted ionization dominates solvolytic reactions of 2-methyl-2-methoxy-1-propyl bromobenzenesulfonate (VII).[19] MeO-3-assisted ionization is also important in other cases.[20]



VII

The variation of k/k_s values with solvent in solvolysis of $MeO(CH_2)_4OBs$ and $Me(CH_2)_5OBs$ is instructive. As is clear from Table 1, k/k_s is lowest in ethanol, the most nucleophilic solvent. Thus, with $MeO(CH_2)_5OBs$, the use of ethanol as solvent makes k_s nearly as large as k_Δ. The position of alcohol in the solvent sequence of k/k_s or $(1 + k_\Delta/k_s)$ values is actually determined by two other solvent sequences, $EtOH > AcOH < HCOOH$ for k_s and $EtOH < AcOH < HCOOH$ for k_Δ.

It is interesting that k/k_s, and thus k_Δ/k_s, is somewhat larger in acetic acid than in formic acid in the case of MeO-5 and MeO-6 participation. This is due to the fact that k_s is more sensitive to the solvent change, $AcOH \rightarrow HCOOH$, than is k_Δ.

α-Methyl and δ-methyl substitution

The effects of α- and δ-methyl groups on MeO-5 participation are of some interest, pertinent data being summarized in Table 4. From the rate comparisons in this table, it is clear that k_Δ/k_s is high in acetolysis for all the 4-methoxy-1-alkyl esters, whether α-, δ-, or α,δ-methyl substituted. However, α-methyl substitution does reduce k_Δ/k_s.

On scrutinizing the relative *k* values (essentially relative k_Δ values) of the 4-methoxyalkyl esters in Table 4, it is seen that a δ-methyl group increases the rate by a factor of 6. For α-methyl substitution either retardation or acceleration is conceivable on theoretical grounds.[11,18] In the present case, an α-methyl group accelerates rate by a factor of 6. This contrasts with the effect of α-methyl substitution on rate of 0–5 ring closure involving a participating benzamido group[6] but agrees with that observed in Ar_1-5 participation.[6]

The effects of σ- and δ-methyl substitution on rate of 0–5 closure by MeO-5 participation are approximately additive with the *threo*-5-methoxy-2-hexyl ester (X).

[17] G. Salomon, *Helv. Chim. Acta* **19**, 743 (1936).
[18] S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.* **70**, 828 (1948).
[19] S. Winstein, C. R. Lindegren and L. L. Ingraham, *J. Amer. Chem. Soc.* **75**, 155 (1953).
[20] For example, S. Winstein *et al.*, *J. Amer. Chem. Soc.* **65**, 2196 (1943); **70**, 821 (1948); **74**, 1160 (1952).

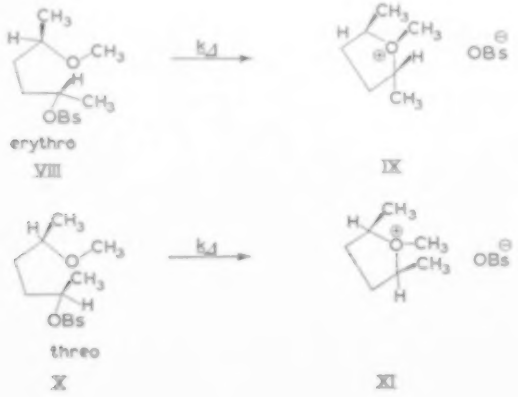
However, the *erythro*-5-methoxy-2-hexyl ester(VIII) is slower than its *threo*-isomer X by a factor of ca. 2·5, this being ascribed most plausibly to a steric retardation. In the cyclic oxonium ion, the methyl groups are *cis* in the intermediate (XI) from the *threo*-diastereomer, while they are *trans* in the intermediate (IX) from the *erythro* isomer.

TABLE 4. RELATIVE RATES OF ACETOLYSIS OF SOME METHYL-SUBSTITUTED BUTYL BROMOBENZENESULFONATES AT 25°

Compound	$\Delta H^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$ (entropy units)	Relative rate	
$CH_3(CH_2)_2CH_2OBs$	23·7	−17·4	1·00	
$CH_3OCH_2(CH_2)_2CH_2OBs$	22·0	−10·4	657	1·00
			(2200)[a]	
$CH_3OCH_2(CH_2)_2CH(OBs)CH_3$	21·1	−9·4	4135[b]	6·29
			$(1·23 \times 10^4)$[a]	
$CH_3OCH(CH_3)(CH_2)_2CH_2OBs$	20·8	−10·9	4111	6·26
			$(1·22 \times 10^4)$[a]	
$CH_3OCH(CH_3)(CH_2)_2CH(OBs)CH_3$				
Erythro	21·0	−8·2	9447[c]	14·38
Threo			$2·28 \times 10^4$[d]	34·70
$CH_3CH_2CH(OBs)CH_3$	23·7	−7·7	140	

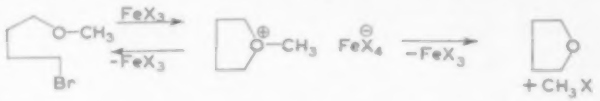
[a] Based on $k^{\circ}_{ext.}$ from special salt effect of lithium perchlorate.
[b] 30 and (ca. 80) relative to sec-BuOBs. For the bromides in 78·5% formic acid at 85°, the factor 36 is given by the data of Oae.[4]
[c] 67 relative to sec.-BuOBs.
[d] 163 relative to sec-BuOBs.

Owing to the pyramidal nature of the oxygen atom in the cyclic oxonium ion, the O-methyl group in the *cis*-intermediate XI can assume a disposition *trans* to both other methyl groups. On the other hand, in the *trans*-intermediate (IX), the O-methyl group must be *cis* to one of the other two methyl groups. This type of interaction could plausibly account for the small reactivity differential between the diastereomeric 5-methoxy-2-hexyl bromobenzenesulfonates (VIII) and (X).

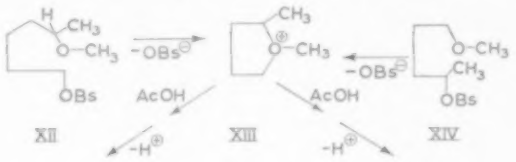


Me–O *and Methylene-O cleavage*

The products of solvolysis by way of MeO-*n* participation may conceivably involve Me–O or Methylene–O cleavage of the cyclic oxonium ion intermediate IV. In MeO-3 participation, we have not observed Me–O cleavage, the strained three-membered ring being cleaved instead.[20] In MeO-5 participation also, Me–O cleavage with resulting formation of tetrahydrofurans VI ($n = 5$) appears to be relatively unimportant.*



For example, from acetolysis of the 4-methoxy-1-pentyl and 5-methoxy-2-pentyl esters (XII) and (XIV) are obtained in very high yield identical mixtures of secondary and primary acetates (XV) and (XVI) in a 60 to 40 ratio. Some Me–O cleavage does



$CH_3OCH(CH_3)CH_2CH_2CH_2OAc$ XV

$CH_3OCH_2CH_2CH_2CH(OAc)CH_3$ XVI

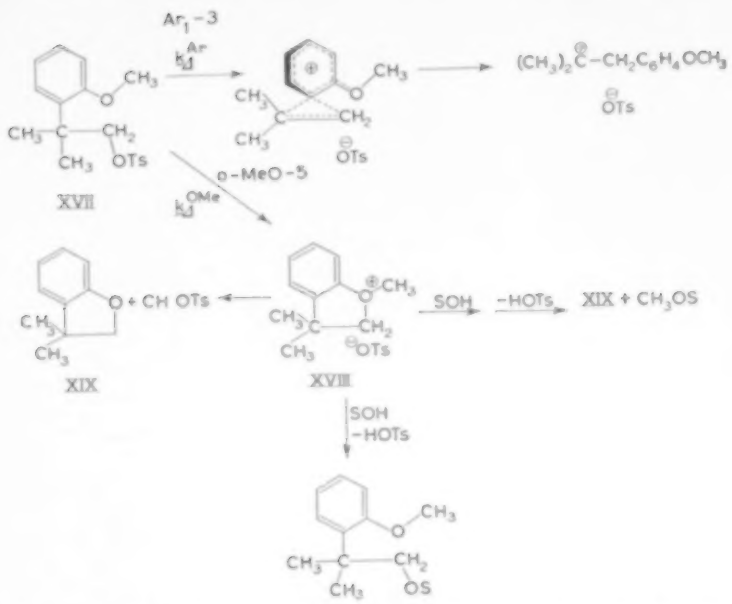
occur in acetolysis of 5-methoxy-1-pentyl bromobenzenesulfonate, this material giving rise to substantial amounts of tetrahydropyran, methyl acetate, methyl bromobenzenesulfonate and 5-methoxy-1-pentyl acetate.

o-MeO *participation*

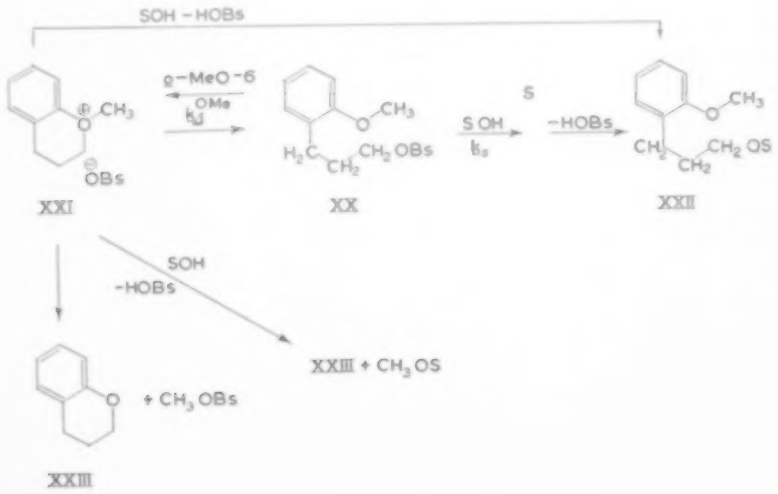
The participating methoxyl group may be an *o*-methoxyl substituent in a phenyl group, as in *o*-methoxyneophyl toluenesulfonate (XVII). As already reported elsewhere,[1,2,21,22] *o*-MeO-5 competes with Ar_1-3 participation in solvolysis of this substrate, anchimerically unassisted solvolysis being negligible. As the data summarized in Tables 5 and 6 show, *o*-MeO-assisted ionization is also important in formolysis and acetolysis of 3-*o*-anisyl-1-propyl bromobenzenesulfonate (XX) and 3-*o*-anisyl-3-methyl-1-butyl toluenesulfonate (XXIV). With these substrates, Ar_1-4 participation may be judged to be negligible by analogy with the behavior of the *p*-isomers.[6,23] Also, k_s the rate constants for anchimerically unassisted solvolysis (process S) may be approximated as equal to the values for the *p*-isomers or even the analogs without the methoxyl substituent.[6,23] On this basis, solvolysis of the 3-*o*-anisyl-1-propyl ester (XX) is largely, and that of the 3-*o*-anisyl-3-methyl-1-butyl derivative (XXIV) is exclusively *o*-MeO-6 assisted. Because of anchimeric assistance, the 3-*o*-anisyl-3-methyl-1-butyl derivative XXIV is more reactive in solvolysis than the *p*-isomer by a factor of ca. 10^4.

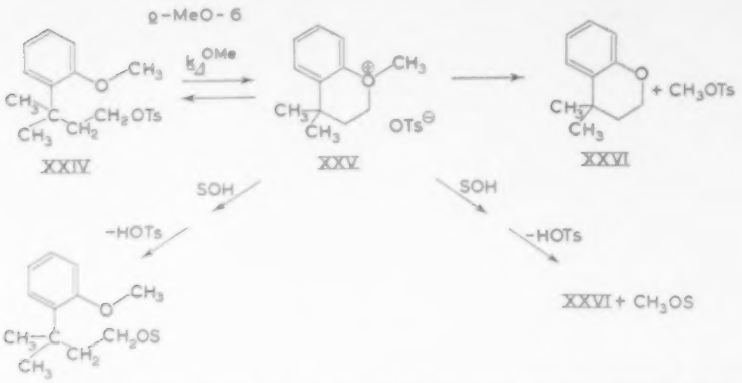
* It is interesting that Kirrmann and Hamaid[5] report a high yield of tetrahydrofuran from treatment of 4-methoxy-1-butyl bromide with ferric chloride. However, this result does not indicate how well Me–O competes with methylene–O cleavage, since the latter is reversible under the conditions employed.

[21] R. Heck, J. Corse, E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.* **79**, 3278 (1957).
[22] S. Winstein in G. R. Robertson, *Modern Chemistry for the Engineer and Scientist* Chap. 7. McGraw-Hill, New York (1957).
[23] R. Heck, unpublished work.

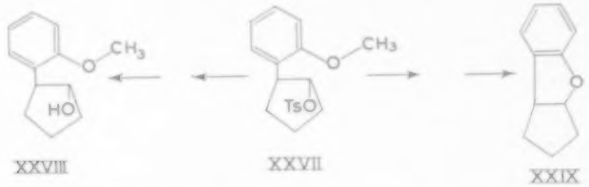


As regards the mode of cleavage of the intermediate cyclic oxonium ion intermediates from ionization of the *o*-anisyl-1-alkyl derivatives XVII, XX and XXIV, Me–O cleavage is important in all three cases. In solvolysis of the two derivatives with the *gem.*-Me_2 grouping, Me–O cleavage is almost exclusive, and this gives rise to 3,3-dimethyl-4,5-benzodihydrofuran (XIX) and 4,4-dimethyl-2,3-dihyrobenzopyran (XXVI) as products. In formolysis of the 3-*o*-anisyl-1-propyl ester XX, without the *gem.*-Me_2 grouping, methylene–O cleavage of the intermediate XXI competes nearly equally with Me–O cleavage. From the latter is obtained the benzodihydropyran XXIII.

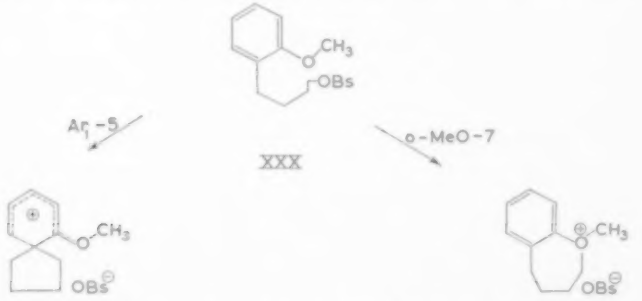




o-MeO-5 participation in solvolytic substitution may be illustrated further with the example of acetolysis of *trans*-2-*o*-anisyl*cyclo*pentyl toluenesulfonate (XXVII). This material acetolyzes[23,24] at a rate eight times that of the *p*-isomer[23,25] at 50°, even though acetolysis of the latter material is already anchimerically accelerated owing to Ar_1-3 participation.[23] At least some of the excess solvolysis rate of the *o*-isomer XXVII compared to the *p*-derivative is due to *o*-MeO-5 participation, since the cyclic ether XXIX is obtained along with *trans*-2-*o*-anisyl*cyclo*pentanol (XXVIII) in yields of 22 and 64 per cent, respectively, from acetolysis of the *o*-isomer (XXVII) and subsequent treatment of the reaction product with lithium aluminum hydride.



In solvolysis of 4-*o*-anisyl-1-butyl *p*-bromobenzenesulfonate (XXX), *o*-MeO participation would necessarily be *o*-MeO-7. However, as illustrated in Tables 5 and 6, the 4-*o*-anisyl-1-butyl ester (XXX) displays almost the same formolysis and



acetolysis rate constants as does the *p*-isomer.[6] If the k_s and k_Δ^{Ar} values are approximated as equal to those of the *p*-isomer, the k_Δ^{OMe} value turns out to be zero in acetolysis

[24] A Fainberg, unpublished work.
[25] A. H. Fainberg, G. C. Robinson and S. Winstein, *J. Amer. Chem. Soc.* **78**, 2777 (1956).

TABLE 5. *o*-MeO PARTICIPATION IN FORMOLYSIS OF *o*-ANISYLALKYL ARENESULFONATES

Compound	Temperature (°C)	Rate constants (sec^{-1})				% Reaction by				
								o-MeO		
		Total 10^5k	10^5k_s	$10^5k_\Delta^{Ar}$	$10^5k_\Delta^{OMe}$	Ar_1	*S*	Total	CH_3–O cleavage	Me–O cleavage
$(CH_3)_2C(o\text{-}CH_2OC_6H_4)CH_2OTs$	25·0	13·3	ca. 0	9·8	3·5	73	0	27	small	ca. 27
$o\text{-}CH_3OC_6H_4CH_2CH_2CH_2OBs$	75·0	39·7	2·0[c]	—	37·7	—	5	95	46	49
	50·0	3·45[b]	0·15[c]	—	3·30					
	25·0	0·20[c]	0.01[c,c]	—	0·19					
$(CH_3)_2C(o\text{-}CH_2OC_6H_4)CH_2CH_2OTs$	25·0	22·0	ca. 0	—	22·0	—	0	100	<5[d]	>95
$o\text{-}CH_3OC_6H_4CH_2CH_2CH_2CH_2OBs$	75·0	7·14	2·8[c]	3·3[c]	1·0(?)					

[a] Based on the 3-phenyl-1-propyl derivative.[6]
[b] $\Delta H\pm = 21{\cdot}2$ kcal/mole; $\Delta S\pm = -13{\cdot}6$ entropy units.
[c] Extrapolated from the data at the other temperatures.
[d] Upper limit because the liquid toluenesulfonate may have contained the alcohol as a contaminant.
[e] Based on the *p*-isomer.[6]

and a value in formolysis of about one-fortieth of that for *o*-MeO-6. In any case, *o*-MeO-7 participation does not compete substantially with anchimerically unassisted and Ar_1-5-assisted processes.

It is interesting that steric factors contrive to make the rate sequence *o*-MeO-6 > *o*-MeO-5, at least with the *o*-anisyl-1-alkyl derivatives with the *gem*.-Me_2 grouping. This is the reverse of the sequence observed in MeO-*n* participation, MeO-5 > MeO-6 The *gem*.-Me_2 grouping has a large effect on k_Δ^{OMe} for both *o*-MeO-5 and *o*-MeO-6 participation. For *o*-MeO-5 this is clear from the comparison of *o*-methoxyneophyl and 2-*o*-anisyl-1-ethyl toluenesulfonates.[21] For *o*-MeO-6, the comparison of k_Δ^{OMe} values for the 3-*o*-anisyl-1-propyl and 3-*o*-anisyl-3-methyl-1-butyl esters (XX; XXIV) shows that the *gem*.-Me_2 grouping increases k_Δ^{OMe} by a factor greater than 10^2.

It is interesting to cross-compare rates of MeO-assisted and *o*-MeO-assisted ionizations, since the *o*-anisyl derivatives have a less nucleophilic methoxyl group, but also greater conformational restrictions than their aliphatic counterparts. The k_Δ^{OMe} values for the 5-methoxy-1-pentyl and 3-*o*-anisyl-1-propyl bromobenzenesulfonates show MeO-6-assisted ionization to be faster than *o*-MeO-6 by a factor of only ca. 3 in formic acid at 75°. The rate of *o*-MeO-5-assisted ionization of the *o*-methoxyneophyl derivative XVII, with the *gem*.-Me_2 grouping, is nearly equal to that of MeO-5-assisted ionization of 4-methoxy-1-butyl toluenesulfonate.

Kinetics and ion pair return in acetolysis

The behavior of the cyclic oxonium ion intermediates as ion pairs[2,25,26–33] determines some interesting kinetic features of the acetolysis of the substrate systems solvolyzing with methoxyl participation. However, we cannot yet describe the number and nature of the various ion-pair varieties which may be involved.[26–33]

In those cases where Me–O cleavage occurs, ion-pair return[30] produces methyl

[26] W. G. Young, S. Winstein and H. L. Goering, *J. Amer. Chem. Soc.* **73**, 1958 (1951).
[27] S. Winstein and K. C. Schreiber, *J. Amer. Chem. Soc.* **74**, 2165 (1952).
[28] C. A. Grob and S. Winstein, *Helv. Chim. Acta.* **35**, 782 (1952).
[29] S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, *J. Amer. Chem. Soc.* **76**, 2597 (1954); *Chem. & Ind. (Rev.)* 664 (1954).
[30] S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, *J. Amer. Chem. Soc.* **78**, 328 (1956).
[31] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.* **78**, 2767 (1956).
[32] S. Winstein and G. C. Robinson, *J. Amer. Chem. Soc.* **80**, 169 (1958).
[33] S. Winstein and A. H. Fainberg, *J. Amer. Chem. Soc.* **80**, 459 (1958).

TABLE 6. *o*-MeO PARTICIPATION IN ACETOLYSIS OF *o*-ANISYLALKYL ARENESULFONATES

Compound	Temperature (°C)	Rate constants (sec^{-1})				Reaction (per cent) by						
						Ar_1	S	*o*-MeO				
								Total	CH_3–O Cleavage		CH_2–O Cleavage	
		Total 10^5k	10^5k_s	$10^5k_\Delta^{Ar}$	$10^5k_\Delta^{OMe}$				No ion pair return	Ion pair return	Ion pair return	No ion pair return
$(CH_3)_2C(o\text{-}CH_3OC_6H_4)CH_2OTs$	75·0[a]	48	ca. 0	11	37	25	0	75	4	ca. 0[b]	40	31
$o\text{-}CH_3OC_6H_4CH_2CH_2CH_2OBs$	75·0	0·91[c]	0·11[d]	—	0·80	—	12	88		24[b]	29	
$(CH_3)_2C(o\text{-}CH_3OC_6H_4)CH_2CH_2OTs$	75·0	56·2[e]	0·01[f]	—	56·2	—	0	100		small[b]	ca. 65	
$o\text{-}CH_3OC_6H_4CH_2CH_2CH_2CH_2OBs$	75·0	0·18	0·14[d]	0·05[d]	—							
	100·0	2·10[g]										

[a] Solvent contained 0·031 N sodium acetate.
[b] Assuming all ion pair return is eliminated by lithium perchlorate.
[c] k°_{ext} from runs with added lithium perchlorate.
[d] Based on the *p*-isomer.[6]
[e] Initial first-order rate constant for disappearance of toluenesulfonate.
[f] Based on the *p*-isomer.[23]
[g] $\Delta H^{\pm} = 24{\cdot}7$ kcal/mole; $\Delta S^{\pm} = -14{\cdot}3$ entropy units.

toluenesulfonate or bromobenzenesulfonate, as the case may be. Thus, during acetolysis of *o*-methoxyneophyl toluenesulfonate(XVII), methyl toluenesulfonate is formed.[2,21] Since the latter material is very much less reactive in acetolysis than the *o*-methoxyneophyl derivative, a relatively steady infinity acid titer, 60 per cent of theoretical, is observed, unaffected by the inclusion of lithium toluenesulfonate to the acetolysis solution.[2] By the use of this infinity acid titer, good first-order kinetics are obeyed by *o*-methoxyneophyl toluenesulfonate in the production of acid.[21] The derived first-order rate constant in this case is for disappearance of *o*-methoxyneophyl toluenesulfonate(XVII), inclusive of the reaction which produces methyl toluenesulfonate. Quite analogously, the first-order rate constant obtained for acetolysis of 5-methoxy-1-pentyl bromobenzenesulfonate includes formation of methyl bromobenzenesulfonate to the extent of 57 per cent at 50° and 54 per cent at 75°.

In the case of 3-*o*-anisyl-1-propyl bromobenzenesulfonate (XX), the methyl ester formed during acetolysis solvolyzes at a rate not far below that of the original ester. Kinetic analysis, making use of the measured rate constant for acetolysis of the methyl ester, furnishes first-order rate constants for solvolysis and formation of methyl bromobenzenesulfonate, respectively.

Formation of methyl toluenesulfonate also accompanies acetolysis of 3-*o*-anisyl-3-methyl-1-butyl toluenesulfonate (XXIV). Further, solvolysis of the methyl ester is slower than that of the original ester by a very large factor. However, the kinetics observed in this case are not as simple as those employed by the *o*-methoxyneophyl system. With the 3-*o*-anisyl-3-methyl-1-butyl system, first-order constants drift down in a run, and the 34 per cent acid infinity titer observed in acetolysis at 75° is appreciably decreased by addition of lithium toluenesulfonate to the acetolysis solution. Evidently, methyl toluenesulfonate formation involves more than ion-pair return[30] in this case.

Good first-order kinetics of acetolysis, without the complication of appreciable methyl arenesulfonate formation, are displayed by the other substrate systems solvolyzing with MeO-participation. With the exception of the 3-*o*-anisyl-3-methyl-1-butyl system XXIV, no common ion rate depression[30], is visible in acetolysis of the various substrates. The actual addition of lithium bromobenzenesulfonate in acetolysis of the 4-methoxy-1-butyl, 4-methoxy-1-pentyl and 5-methoxy-2-pentyl systems failed also to produce any common ion rate depression. Evidently, return of dissociated oxonium ion intermediate to covalent starting material is unimportant with nearly all the systems investigated.

Ion-pair return accompanying acetolysis of the methoxy-substituted alkyl arenesulfonates is very subject to added lithium perchlorate or other salts, such as lithium or sodium acetate.[26–33] While it is not yet clear whether the added salts eliminate all ion-pair return,[26–33] it is clear that the portion of ion-pair return that produces methyl arenesulfonate is essentially completely eliminated. Thus, inclusion of lithium perchlorate or acetate in acetolysis of *o*-methoxyneophyl toluenesulfonate (XVII) brings the infinity acid titer essentially up to the theoretical value. The concentration of lithium perchlorate, symbolized by $(LiClO_4)_{1/2}$, which half eliminates methyl toluenesulfonate formation is 0·003 M (Table 7). In the other acetolyses, which are accompanied by production of methyl arenesulfonate, formation of the latter is eliminated by the inclusion of lithium perchlorate. With 3-*o*-anisyl-1-propyl bromobenzenesulfonate (XX), this eliminates the downward drift in the first-order rate constant observed in acetolysis, good first-order kinetics now being observed.

TABLE 7. SUMMARY OF LITHIUM PERCHLORATE SPECIAL SALT EFFECTS IN ACETOLYSIS

Compound	Temperature (°C)	b	$(LiClO_4)_{1/2}$ 10^4M	$k^\circ_{ext.}/k^\circ_t$
$CH_3OCH_2(CH_2)_2CH_2OBs$	50·0	8·4	8	2·76
	75·0	6·8		2·32
$CH_3OCH(CH_3)(CH_2)_2CH_2OBs$	25·2	9·0	0·9	2·97
$CH_3OCH_2(CH_2)_2CH(CH_3)OBs$	25·2	12·5	0·9	2·98
erythro-$CH_3OCH(CH_3)(CH_2)_2CH(CH_3)OBs$	25·2	13		2·93
3-*o*-Anisyl-1-propyl OBs	75·0	5		2·1
o-Methoxyneophyl OTs	75·0		30[a]	
trans-2-*o*-Anisyl*cyclo*-pentyl OTs	25·0	16		2·6
	50·0	15		2·1

[a] Lithium perchlorate concentration that half eliminates formation of methyl toluenesulfonate during acetolysis.

The effect of appreciable concentrations of added lithium perchlorate on solvolysis rate sheds light on the magnitude of ion-pair return to methylene carbon atoms which is eliminated by added salt. Such ion-pair return eliminated by lithium perchlorate is not serious in the case of the two systems containing the *gem*.-Me_2 grouping, namely *o*-methoxyneophyl (XVII) and 3-*o*-anisyl-3-methyl-1-butyl (XXIV). Similarly, it is not serious with the 5-methoxy-1-pentyl derivative. It is, however, important with the 3-*o*-anisyl-1-propyl system (XX) and the other derivatives that solvolyze with methoxyl participation. The magnitude of ion-pair return at both methylene and methyl carbon atoms during acetolysis of the 3-*o*-anisyl-1-propyl derivative(XX) is summarized in Table 6.

In acetolysis of the derivatives displaying ion-pair return to the methylene position which is affected by added lithium perchlorate, the addition of this salt gives rise to the steep special[26–33] salt effects at low concentrations and the more shallow normal[26–33] linear salt effects at high concentrations. In Table 7 are listed the values of the measure of the magnitude of the special salt effects, namely k°_{ext}/k°_t. In this ratio, k°_{ext} is the solvolysis rate constant that includes the special but excludes the normal salt effects.[26–33] It is a closer approximation to $(k_s + k_\Delta)$ than is k°_t, the solvolysis rate constant in the absence of added lithium perchlorate. Also listed in Table 7 are some values of $(LiClO_4)_{1/2}$, the concentration of lithium perchlorate that produces one-half of the total special salt effect. The normal portion of the lithium perchlorate salt effects is summarized in Table 7 with the aid of the b values from the fit of the data to the linear relation given in equation (3).

$$k_t = k^\circ_{ext}\,[1 + b\,(LiClO_4)] \qquad (3)$$

Exchange accompanying solvolysis is another aspect of the acetolysis of the present derivatives that helps to place them in the whole spectrum of systems in acetolysis of which ion pairs are important.[26–33] While lithium bromobenzenesulfonate fails to depress rate of acetolysis of the 4-methoxy-1-pentyl and 5-methoxy-2-pentyl bromobenzenesulfonates, inclusion of lithium toluenesulfonate causes relatively efficient conversion of bromobenzenesulfonate to toluenesulfonate during acetolysis. The situation here resembles that presented by the 3-*p*-anisyl-2-butyl system[30,32], exchange occurring by way of ion pairs. In other respects also (Table 7), acetolysis of the present derivatives resembles that of the 3-*p*-anisyl-2-butyl[30,32] 1-*p*-anisyl-2-propyl[30,33] or 2-*p*-anisyl-1-ethyl[31,34] systems.

[34] P. Klinedinst and E. Jenny, unpublished work.

Tetrahedron, 1958, Vol. 3, pp. 14–27. Pergamon Press Ltd., London

STEROIDS—XCII*

SYNTHESIS OF HALOGENATED STEROID HORMONES—II†

6α- AND 6β-FLUOROTESTOSTERONE AND 6α- AND 6β-FLUOROPROGESTERONE

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(*Received* 14 *November* 1957)

Abstract—Fission of 3β-acetoxy-5α,6α-epoxides in the cholestane, androstane and pregnane series with boron trifluoride etherate afforded the corresponding 3β-acetoxy-5α-hydroxy-6β-fluoro compounds.[1] By appropriate manipulation of these fluorohydrins 6α-fluorocholestenone and the biologically interesting 6α- and 6β-fluorotestosterone and 6α- and 6β-fluoroprogesterone were prepared.

INTEREST in fluoro steroids has been greatly stimulated during the last 3 years following the demonstration by Fried and Sabo[2] that 9α-fluorohydrocortisone has approximately eleven times the glucocorticoid activity of hydrocortisone and is highly effective in maintaining life in the adrenal insufficient rat,[3] dog,[4] and man.[4,5]

Extension of this finding to other series of compounds has fully confirmed the remarkable effect of the 9α-fluorine atom on biological activity. 9α-Fluorocorticosterone acetate[6] and 9α-fluorodehydrocorticosterone acetate[6] possess mineralocorticoid activity of the order of that observed with aldosterone. 9α-Fluoro-11β-hydroxy and 11-keto-progesterone have been shown[6] to have approximately the same glucocorticoid activity as cortisone acetate and 1-dehydro-9α-fluorohydrocortisone[7,8] and 6-dehydro-9α-fluorohydrocortisone[7] both have considerably enhanced glucocorticoid and salt retaining activities compared to the corresponding non-fluorinated compound. 2-Methyl-9α-fluorohydrocortisone acetate[9] exhibits thirty-eight times the activity of hydrocortisone in the glycogen deposition assay and is ninety times more potent than deoxycorticosterone acetate in the salt retention assay.[9]

It was pointed out recently[10] that the enhancement of adrenocorticoid activity by introduction of a 9α-substituent is paralleled by the electronegativity of the

* Paper XCI. A. Bowers, C. Casas Campillo and Carl Djerassi *Tetrahedron* **2**, 165 (1958).
† Part I. H. J. Ringold, E. Batres, O. Mancera and G. Rosenkranz *J. Org. Chem.* **21**, 1432 (1956).
‡ This reference gives a detailed discussion of fission of 3β-acetoxy-5α,6α-epoxides with boron trifluoride. We are very grateful to Dr. H. B. Henbest, Kings College, London, for a copy of this manuscript prior to publication.

[1] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).‡
[2] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **76**, 1455 (1954).
[3] A. Borman, F. M. Singer and P. Numerof, *Proc. Soc. Exp. Biol. Med.* **86**, 570 (1954).
[4] G. W. Liddle, M. M. Pechet and F. C. Bartter, *Science* **120**, 496 (1954).
[5] A. Goldfien, G. W. Thorn, P. M. Beigleman and J. C. Laidlaw, *J. Clin. Endroclin.* **14**, 782 (1954).
[6] J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *J. Amer. Chem. Soc.* **77**, 1068 (1955).
[7] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *J. Amer. Chem. Soc.* **77**, 4181 (1955).
[8] R. F. Hirshmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *J. Amer. Chem. Soc.* **77**, 3166 (1955).
[9] J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *J. Amer. Chem. Soc.* **77**, 6401 (1955).
[10] J. E. Herz, J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **78**, 2017 (1956).

9α-substituent, the effect being greatest with 9α-fluorine atom. These authors suggested that this effect may be due to an increase in the acidity constant of the 11β-hydroxyl group brought about by the inductive effect of the neighboring 9α-substituent. This hypothesis receives support by the reported activity of 12α-fluoro-11β-hydroxyprogesterone[8] and 12α-fluorocorticosterone[11] since both compounds show biological activity of the same order as their corresponding 9α-fluoro isomers.

Further interest was stimulated in fluoro steroids when it was shown[12] that 21-fluoroprogesterone is a potent progestational hormone being two to four times as active as progesterone and that introduction of a 21-fluorine atom into various cortical hormones enhances the glucocorticoid activity of the corresponding 21-deoxy compounds by approximately three to five times.[13]

In view of these remarkable biological findings it seemed desirable to investigate the synthesis of steroid hormone analogs with fluorine substituents in positions other than 9, 12 and 21.

It has been shown in these laboratories[14] and elsewhere[15] that introduction of a 6-methyl group favorably affects the biological activity of testosterone,[14] and progesterone[14] as well as glucocorticoids[15] and consequently the corresponding 6-fluoro compounds might be expected to be of biological interest.

A suitable system for the introduction of a fluorine atom at C-6 appeared to be the 5α,6α-epoxide since by analogy with the diaxial cleavage of a 9β,11β-epoxide or an 11β,12β-epoxide[11,12] one would expect to obtain the 6β-fluoro-5α-hydroxy compound from hydrogen fluoride fission. However under various experimental conditions[16] * we were not able to convert in reasonable yield a 3β-acetoxy 5α,6α-epoxide system to the corresponding fluorohydrin with anhydrous hydrogen fluoride and in view of our success with the boron trifluoride approach described below this reaction was not investigated further.

Treatment of a solution of cholesterol α-epoxide (Ia) (Fig. 1) or cholesterol acetate α-epoxide (Ib) in an ether–benzene mixture with an excess of boron trifluoride etherate[1] for 3 hr at room temperature afforded in good yield the corresponding 5α-hydroxy-6β-fluoro compound IIa or IIb. Acetylation of IIa readily gave IIb and lithium aluminum hydride hydrolysis of IIb afforded IIa in good yield.

Oxidation of the 6β-fluoro-diol (IIa) with 8 N chromic acid in acetone[17] smoothly afforded the C-3 ketone (III) which underwent acid catalyzed dehydration with hydrogen chloride in acetic acid to afford 6α-fluorocholestenone (IV). A discussion of the proof that this dehydration is attended by concomitant epimerization of the fluorine atom is deferred until the experimental evidence available from the transformations in the androstane series is described.

The following reaction sequences (I → IV) clearly demonstrated a feasible route to 6-fluoro-Δ^4-3-ketones in the biologically more interesting androstane and pregnane

* For detailed discussions of the factors involved in the fission of steroid epoxides with hydrogen fluoride see Hirschmann *et al.* and Fried and Sabo.

[11] D. Taub, R. D. Hoffsommer and M. L. Wendler, *J. Amer. Chem. Soc.* **78**, 2912 (1956).
[12] P. Tannhauser, R. J. Pratt and E. V. Jensen, *J. Amer. Chem. Soc.* **78**, 2658 (1956).
[13] J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *J. Amer. Chem. Soc.* **78**, 4812 (1956).
[14] H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.* **22**, 99 (1957).
[15] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).
[16] R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *J. Amer. Chem. Soc.* **78**, 4956 (1956); J. Fried and E. F. Sabo *Ibid.* **79**, 1130 (1957).
[17] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).

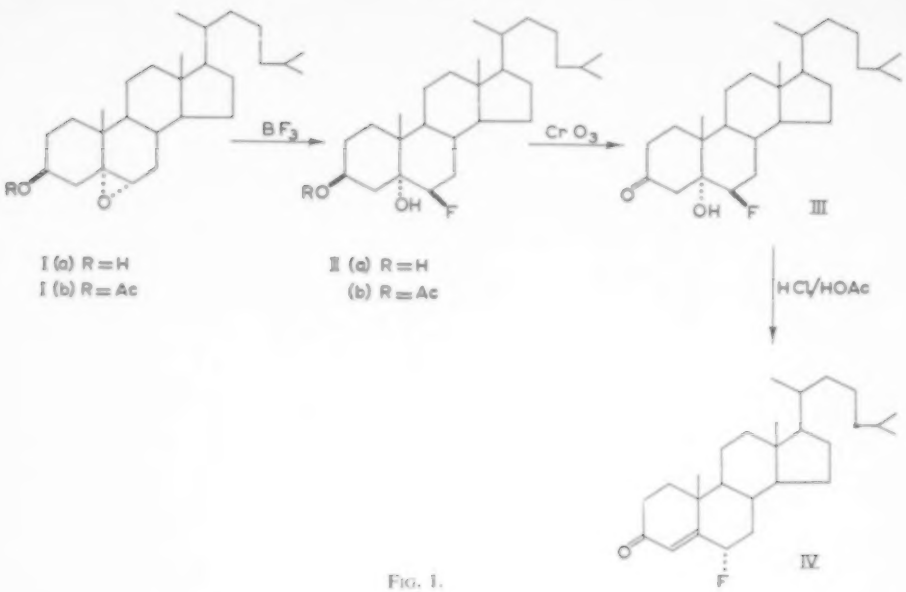

FIG. 1.

series. By application of this method for the introduction of a 6-fluorine atom and appropriate manipulation of the fluorohydrins we were able to synthesize 6α- and 6β-fluorotestosterone and 6α- and 6β-fluoroprogesterone.

Our starting material in the androstane series was the readily available Δ^5-androstene-3β,17β-diol-diacetate (V) (Fig. 2) which with permonophthalic acid afforded the α-epoxide (VI) in 70 per cent yield.*

Using the conditions developed in the cholesterol series the α-epoxide (VI) was cleaved with borontrifluoride etherate to the fluorohydrin (VII) in 80 per cent yield (allowing for recovered starting material). Lithium aluminum hydride hydrolysis of the acetyl groups of VII smoothly gave the 6β-fluoro-triol (X), which was oxidized in good yield to the corresponding 3,17-diketone (XIII). Dehydration of this β-hydroxyketone (XIII) with anhydrous hydrogen chloride in acetic acid smoothly afforded the 6α-fluoro-Δ^4-3,17 diketone (XVI) (see below for a discussion of the configuration of fluorine atom). Lithium aluminum hydride reduction of XVI gave a product having no maximal absorption in the ultraviolet and which probably was a mixture of two diols (XV), both containing a 17 β-hydroxyl group but being epimeric at C-3.[18]† The total reduction product however without purification was oxidized with manganese dioxide[19]‡ to afford 6α-fluorotestosterone (XIV), λ_{max} 236–238 mμ log ε, 4·17.

* An attempt was made to increase the yield of α-epoxide by carrying out the reaction at −60° and then allowing the reaction mixture to warm up to 0° during 16 hr. It was felt that at this low temperature the ratio of the sterically unfavorable β-epoxidation to α-epoxidation would be less than at 0°, which is the more usual temperature for reactions of this type. Although a quantitative study was not carried out, higher yields were obtained (70 per cent) at −80° than at 0°.

† Lithium aluminum hydride reductions of Δ^4-3-ketones are known to give a mixture of C-3 epimeric alcohols. See, for example, McKennis and Gaffney and Plattner *et al.*

‡ For the use of manganese dioxide as a specific oxidizing agent for allylic alcohols see Sondheimer *et al.*

[18] McKennis and Gaffney, *J. Biol. Chem.* **175,** 217 (1949); P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **32,** 265 (1949).

[19] F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* **75,** 5930 (1953).

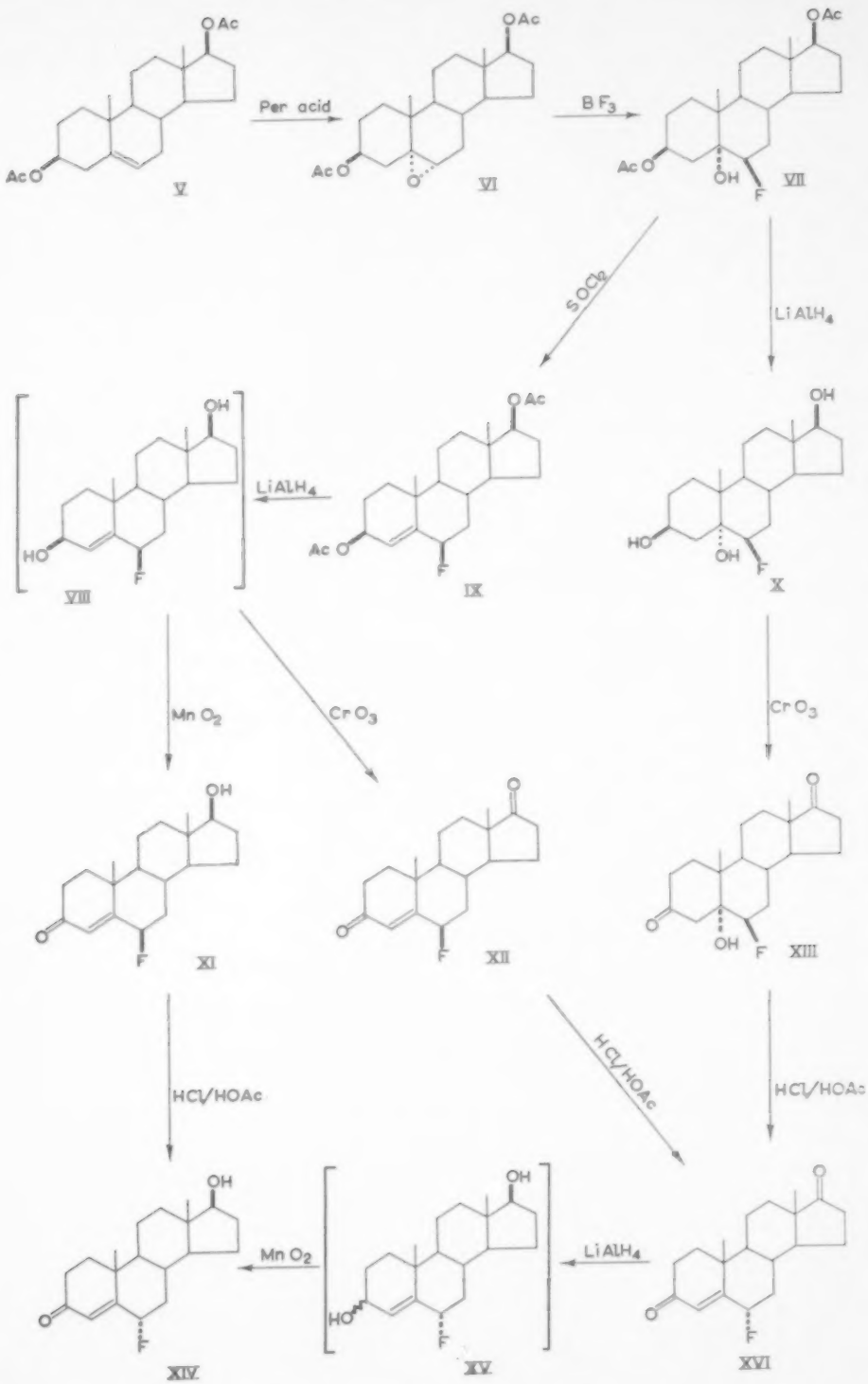
OAc
AcO
V
Per acid
VI
BF_3
OH
F
VII
$SOCl_2$
$LiAlH_4$
HO
VIII
IX
X
MnO_2
CrO_3
O
XI
XII
XIII
HCl/HOAc
XIV
XV
XVI

FIG. 2.

A route to the epimeric 6β-fluorotestosterone was then developed from the fluorohydrin (VII). Thionyl chloride dehydration of VII smoothly gave a compound which had lost the elements of water and which was formulated as the Δ^4-3β-acetate (IX) on the following grounds. The fluoro-diol (VIII) obtained by lithium aluminum hydride hydrolysis of IX, was smoothly converted to a 6-fluorotestosterone (XI) by manganese dioxide oxidation. Compound XI was different from 6α-fluorotestosterone (XIV) and also the fluoro-diketone (XII) from 8 N chromic acid oxidation of VIII was not identical with XVI.

Henbest and Wrigley[1] have unequivocably demonstrated the 5α-hydroxy-6β-fluoro stereochemistry for the fluorhydrin resulting from the boron trifluoride opening of a 3β-acetoxy-5α,6α-epoxide. Consequently (XI) must have the 6β-fluoro configuration, since the reaction sequence VII $\rightarrow$ IX $\rightarrow$ VIII $\rightarrow$ XI would not be expected to be accompanied by inversion at C_6 at any stage. Inversion at C_6 would necessitate abstraction of the 6α-hydrogen atom by either formation of the Δ^5-double bond during the thionyl chloride dehydration followed by rearrangement to the Δ^4-compound or by enolization of the Δ^4-3-ketone (XI) during the manganese dioxide oxidation. We consider both processes to be unlikely. However, the 6β-fluoro substituent is 1,3-diaxially situated with respect to the C-19 methyl group and the resulting non-bonded interactions will certainly make this a less stable arrangement than the corresponding 6α-epimer. Under enolizing conditions the axial 6β-fluoro-Δ^4-3-ketones would be expected to epimerize at C_6. This is in fact the case, and treatment of both XI and XII with hydrogen chloride in acetic acid smoothly gave the 6α-fluoro compounds XIV and XVI respectively.

Further confirmation of the structure assignments comes from an inspection of the molecular rotation differences between the two pairs of compounds XI and XIV, and XII and XVI differing only in the configuration of the fluorine at C_6. Barton and Miller[20] have previously commented on the difference in rotation between epimeric 6α- and 6β-bromo and 6α- and 6β-chloro cholestenones and it can be seen that the 6α-halo-Δ^4-3-ketones are always much more dextrorotatory than their 6β-epimers. This difference is enhanced even more in the 6-fluoroandrostane and pregnane series (Table 1).

A logical extension of this work was application of the same type of reaction sequence to pregnenolone acetate (XVII) (Fig. 3).

Using the low-temperature epoxidation technique, pregnenolone acetate α-epoxide (XVIII) was prepared in 70 per cent yield. Cleavage with boron trifluoride etherate gave the fluorohydrin (XIX), which underwent reduction and hydrolysis to the fluoro-triol (XXII) with lithium aluminum hydride. Oxidation of this triol (XXII) with 8 N chromic acid in acetone gave the 6β-fluoro-5α-hydroxy-3,20-diketone (XXV), which then underwent acid catalyzed dehydration to 6α-fluoroprogesterone (XXIV).

6β-Fluoroprogesterone (XXVI) was prepared by two alternative routes. The first and most direct route involved the alkaline dehydration of the 6β-fluoro-5α-hydroxy-3-ketone (XXV). When XXV was treated with a 0·25 per cent solution of potassium hydroxide in methanol it was possible to isolate 6β-fluoroprogesterone as the major product of the reaction. The 6β-stereochemistry of the fluorine atom

[20] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* **72**, 1066 (1950).

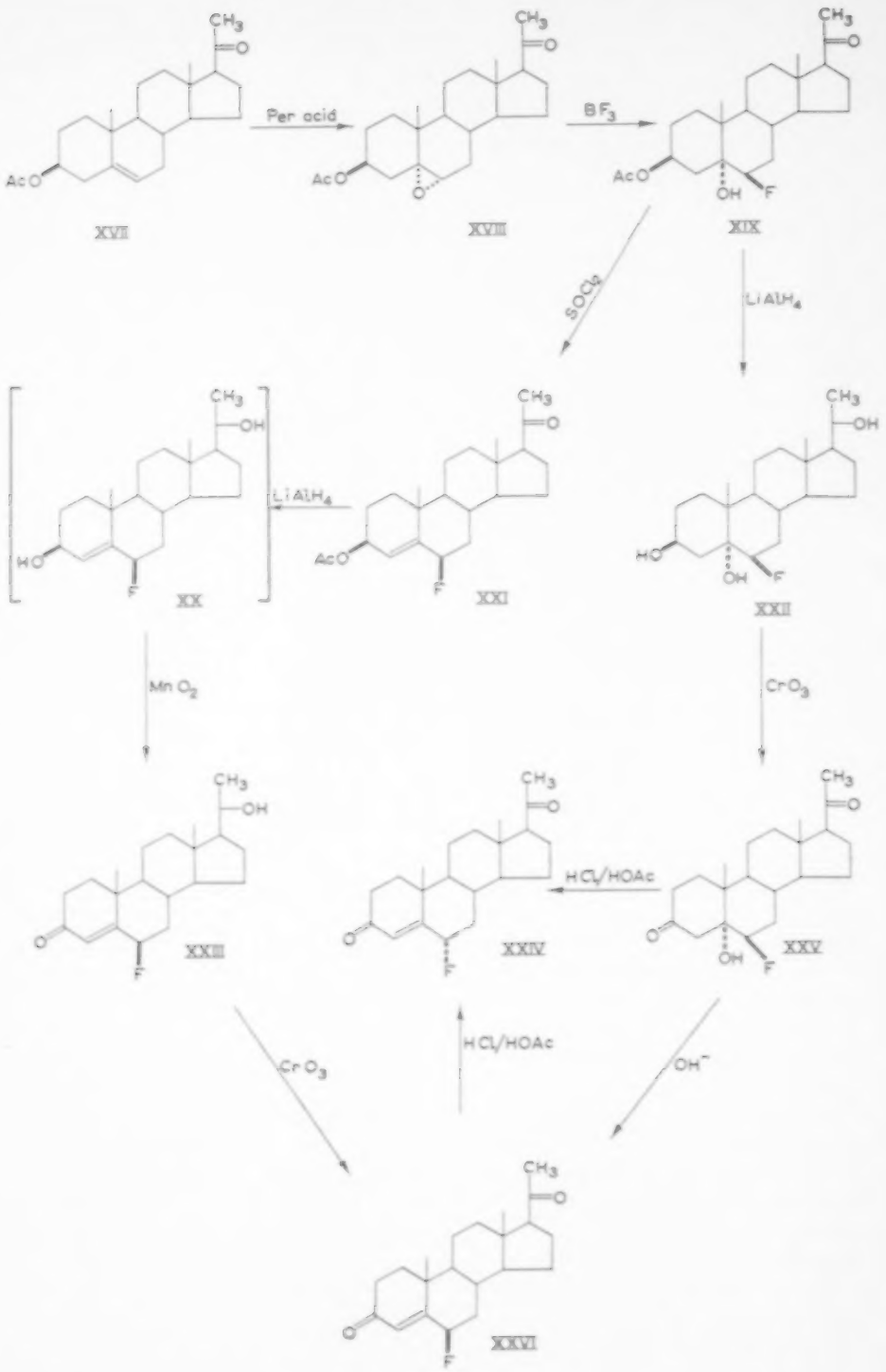
CH3
O
AcO
Per acid
BF3
OH
F
XVII
XVIII
XIX
SOCl2
LiAlH4
HO
XX
XXI
XXII
MnO2
CrO3
XXIII
XXIV
XXV
HCl/HOAc
XXVI
OH⁻

FIG. 3.

Table 1. Molecular rotation data of epimeric 6-halo steroids

Compound	$[M]_D^*$	$\Delta[M]_D$ (6α − 6β)
6α-bromocholestenone	+245†	+217
6β-bromocholestenone	+28†	
6α-chlorocholestenone	+247‡	+182
6β-chlorocholestenone	+65‡	
6α-fluoro-Δ⁴-androstene-3,17-dione (XVI)	+561§	+327
6β-fluoro-Δ⁴-androstene-3,17-dione (XII)	+234§	
6α-fluorotestosterone (XIV)	+312§	+312
6β-fluorotestosterone (XI)	0§	
6α-fluoroprogesterone (XXIV)	+660§	+322
6β-fluoroprogesterone (XXVI)	+338§	

* All rotations in chloroform. † Reference 22. ‡ D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* **72**, 370 (1950). § This paper.

was shown by the molecular rotation comparison with its 6α-epimer (XXIV) (Table 1) and its conversion to XXIV by treatment with hydrogen chloride in acetic acid.

An alternative route to 6β-fluoroprogesterone (XXVI) was similar to that developed for the synthesis of 6β-fluorotestosterone (XI), namely, dehydration of a 6β-fluoro-5α-hydroxy-3β-acetoxy system with thionyl chloride in pyridine to the 6β-fluoro-Δ⁴-3β-acetate followed by hydrolysis of the acetate and selective oxidation of the Δ⁴-3β alcohol. (Fig. 2. (VII) → (IX) → (VIII) → (XI).)

However, in contrast to the stereospecific dehydration observed in the testosterone series, treatment of (XIX) with thionyl chloride in pyridine for 5 min at 0° afforded a mixture of epimeric products. Elemental analysis of this mixture indicated that a molecule of water had been lost, but it was not possible to resolve it chromatographically. It was shown, however, to be a mixture of the expected product XXI and an unsaturated Δ⁵-compound. Hydrolysis (3β-acetate) and reduction (20-ketone) of this mixture with lithium aluminum hydride gave a mixture of glycols, the nature of which could be deduced from the following experiments:

(a) Oxidation with manganese dioxide[19] gave a product (λ_{max} 236 mμ, log ε 3·71) corresponding to 40 per cent of a 6β-fluoro-Δ⁴-3-ketone, which could only have arisen from a Δ⁴-3β alcohol.

(b) Oxidation with 8 N chromic acid in acetone under conditions where isomerization of a Δ^5-3-ketone to a Δ^4-3-ketone would not be expected to take place[21] gave a product (λ_{max} 236, log ε 3·80) corresponding to 50 per cent of a 6-fluoro-Δ^4-3-ketone. A trace of alkali raised the log ε to 4·10, indicating that 50 per cent of the reaction mixture was unconjugated Δ^5-3-ketone. These semiquantitative results are best explained by assuming that thionyl chloride dehydration gives an approximately 1 : 1 mixture of the Δ^4-3β acetate (IX) and a Δ^5-3β acetate.

However, it was found possible to utilize these results for a convenient preparation of 6β-fluoroprogesterone (XXVI). The total dehydration product (which contained approximately 40 per cent of XXI) was treated successively with lithium aluminum hydride and manganese dioxide to afford (XXIII), which was readily separated chromatographically from the more polar Δ^5-3β alcohol by-product. Oxidation of XXIII with 8 N chromic acid gave 6β-fluoroprogesterone (XXIV) in an overall yield of 25 per cent from XIX, the product being identical with that obtained by the alkaline dehydration of XXV.

EXPERIMENTAL

Melting points were determined in capillary tubes in sulfuric acid, and are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Mr. E. Avila for these measurements and for the infrared spectra which were obtained with a Perkin Elmer model-21 spectrophotometer with a sodium chloride prism. Neutral alumina refers to alumina which has been suspended in boiling ethyl acetate for 6 hr, filtered and dried at 100°. We are indebted to Miss L. Cuellar and Mr. E. Denot for skilled technical assistance The elemental analyses were carried out by J. F. Alicino, Metuchen, N. Jersey, and A. Bernhardt, Mulheim/Ruhr, Germany.

6β-Fluorocholestane-3β,5α-diol (IIa). (a) Boron trifluoride etherate (5 cm³) was added to a solution of cholesterol-α-epoxide (Ia) (5·0 g) in anhydrous ether–benzene (1 : 1; 500 cm³). After keeping at room temperature for 3 hr the solution was washed with 5% sodium bicarbonate solution, water, and then dried (Na_2SO_4) and evaporated. A solution of the residue in benzene (250 cm³) was absorbed onto neutral alumina (300 g). Elution with benzene–ether (80 : 20; 700 cm³) afforded cholesterol-α-epoxide (1·75 g) m.p. 138–142° undepressed on admixture with starting material. Further elution with ether (1·5 l.) gave 6β-fluorocholestane-3β,5α-diol (IIa) (2·21 g) m.p. 189–202°, raised by several crystallizations from acetone–hexane to 219–221°, $[\alpha]_D$ +36°,

Anal. Calcd. for $C_{27}H_{47}O_2F$: C, 76·7; H, 11·2; F, 4·50. Found: C, 76·5; H, 11·2; F, 4·3.

(b) A solution of 6β-fluorocholestane-3β,5α-diol 3-monoacetate (IIb) (1·5 g) in tetrahydrofuran (150 cm³) was added over a 10 min period to a suspension of lithium aluminum hydride (1·5 g) in tetrahydrofuran (200 cm³). After stirring for a further 10 min at room temperature the excess of reagent was decomposed with ethyl acetate. Hydrochloric acid (2 N, 200 cm³) was then added and the product extracted with ether. The combined ether extracts were washed with water, 5% sodium bicarbonate solution and finally water. Evaporation of the dried ether solution gave 6β-fluorocholestane-3β,5α-diol (IIa) (1·4 g.) m.p. 188–197°, raised by crystallization

[21] C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

from acetone-hexane to 220–221°, $[\alpha]_D$ +31°, undepressed on admixture with a sample prepared as in (a).

6β-Fluorocholestane-3β,5α-diol 3-monoacetate (IIb). (a) Boron trifluoride etherate (1·0 cm³) was added to a solution of cholesterol acetate α-epoxide (1·0 g) in anhydrous ether–benzene (1:1; 100 cm³). After keeping at room temperature for 3 hr the solution was washed with 5% sodium bicarbonate solution, water, and then dried (Na_2SO_4) and evaporated. A solution of the product in benzene–hexane (1 : 1; 50 cm³) was adsorbed onto neutral alumina (50 g). Elution with benzene (400 cm³) gave 6β-fluorocholestane-3β,5α-diol 3-monoacetate (IIb) (470 mg) m.p. 202–207°, raised by three crystallizations from acetone–hexane to 214–216°, $[\alpha]_D$ −20°.

Anal. Calcd. for $C_{29}H_{49}O_3F$: C, 75·0; H, 10·6. Found: C, 75·1; H, 10·9.

(b) Acetylation of 6β-fluorocholestane-3β,5α-diol (IIa) (acetic anhydride-pyridine at room temperature for 16 hr) readily afforded the 3-monoacetate (IIb), m.p. 212–214°, $[\alpha]_D$ −22°, identical with a sample prepared by method (a).

6β-Fluorocholestane-5α-ol-3-one (III). A solution of 6β-fluorocholestane-3β, 5α-diol (IIa) (1·24 g) in acetone (100 cm³) at 0° was treated with an excess of 8 N chromic acid in aqueous sulfuric acid.[17] After 3 min at 0° addition of water and filtration gave 6β-fluorocholestane-5α-ol-3-one (III), m.p. 223–227°, raised by several crystallizations from acetone–hexane to 230–231°, $[\alpha]_D$ +66°. Compound III exhibited no maximal absorption in the ultraviolet.

Anal. Calcd. for $C_{27}H_{45}O_2F$: C, 77·1; H, 10·8; F, 4·5; Found: C, 76·9; H, 10·7; F, 4·5.

6α-Fluoro-Δ⁴-cholestene-3-one (IV). A solution of 6β-fluorocholestane-5α-ol-3-one (III) (300 mg) in acetic acid (50 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 2 hr and then kept at room temperature for an additional 2 hr. Water was added and the product isolated with ether. The combined ether extracts were washed with water, 5% sodium carbonate solution and water and then dried (Na_2SO_4) and evaporated to afford 6α-fluoro-Δ⁴-cholestene-3-one (IV) (280 mg) m.p. 114–118, raised by three crystallizations from hexane to 116–118°, $[\alpha]_D$ +103°, λ_{max} 236–238 mμ, log ε 4·18.

Anal. Calcd. for $C_{27}H_{43}OF$:C, 80·5; H, 10·8; F, 4·7. Found: C, 80·2; H, 10·8; F, 4·5.

5α,6α-Oxidoandrostane-3β,17β-diol diacetate (VI). To a solution of Δ⁵-androstene-3β,17β-diol diacetate (V) (35 g) in chloroform (300 cm³) at −60 to −70° (acetone–CO_2 bath) was added dropwise over 30 min with stirring a solution of per monophthalic acid (30 g) in ether (800 cm³). The mixture was kept at −80° for a further 2 hr and then at 0–5° for 16 hr. Chloroform (300 cm³) was added and the organic phase washed with 5% sodium carbonate solution and water, dried (Na_2SO_4) and evaporated to afford a product which crystallized after the addition of methanol, yielding 5α,6α-oxidoandrostane-3β,17β-diol-diacetate (VI) (26·1 g), m.p. 155–160°, raised by recrystallization from methanol to 166–168° $[\alpha]_D$ −66°, reported,[22] m.p. 165–166°, $[\alpha]_D$ −69°.

6β-Fluoroandrostane-3β,5α,17β-triol 3,17-diacetate (VII). To a solution of 5α,6α-oxidoandrostane 3β,17β-diacetate (VI) (28·7 g) in a mixture of anhydrous benzene–ether (1 : 1; 2860 cm³) boron trifluoride etherate (40 cm³) was added at room temperature. After 3 hr the solution was washed with 5% sodium carbonate

[22] L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta* **27**, 503 (1944).

solution, water, dried (Na_2SO_4) and evaporated to approximately 1 l., when the solution was adsorbed onto neutral alumina (1·5 kg). Elution with benzene (2·2 l.) afforded VI (14·3 g), m.p. 152–156°, identical with starting material. Further elution with benzene–ether (50 : 50; 1500 cm³) gave 6β-fluoroandrostane-3β,5α,17β-triol 3,17-diacetate (VII) (9·8 g), m.p. 195–210°, raised by several crystallizations from acetone–hexane to m.p. 212–214°, $[\alpha]_D$ −24°.

Anal. Calcd. for $C_{23}H_{35}O_5F$: C, 67·3; H, 8·6; F, 4·6. Found: C, 67·0; H, 8·6; F, 4·4.

6β-Fluoroandrostane-3β,5α,17β-triol (X). A solution of 6β-fluoroandrostane-3β, 5α,17β-triol 3,17-diacetate (VII) (5·0 g) in tetrahydrofuran (200 cm³) was added with stirring to a suspension of lithium aluminum hydride (4·0 g) in tetrahydrofuran (150 cm³) at 0° during 15 min. After stirring for a further 15 min at 0–10° the excess of reagent was destroyed with acetone. Hydrochloric acid (2 N, 200 cm³) was added and the product extracted with ether. The combined ether extracts were washed with 2 N hydrochloric acid, water, and dried (Na_2SO_4) and evaporated to afford 6β-fluoroandrostane-3β,5α,17β-triol (X) (4·28 g), m.p. 185–190°, raised by several crystallizations from acetone to 204–207°, $[\alpha]_D \pm 0°$.

Anal. Calcd. for $C_{19}H_{31}O_3 \cdot \frac{1}{2}(CH_3)_2CO$: C, 69·3; H, 9·6. Found: C, 69·3; H, 9·7.

6β-Fluoroandrostane-5α-ol-3,17-dione (XIII). To a solution of 6β-fluoroandrostane-3β,5α,17β-triol (X) (2·55 g) in acetone (200 cm³) at 0–5° was added dropwise an excess of 8 N chromic acid[17] in aqueous sulfuric acid. After 3 min water was added and the product extracted with ether. The combined ether extracts were washed several times with water, dried (Na_2SO_4) and evaporated to afford 6β-fluoroandrostane-5α-ol-3,17-dione (XIII) (2·05 g), m.p. 217–220°, raised by three crystallizations from acetone–hexane to 231–232° $[\alpha]_D$ +100°. XIII exhibited no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{19}H_{27}O_3F$:C, 70·8; H, 8·4. Found: C, 71·2; H, 8·5.

6α-Fluoro-Δ⁴-androstene-3,17-dione (XVI). (a) A solution of 6β-fluoroandrostane-5α-ol-3,17-dione (XIII) (180 mg) in acetic acid (20 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 1 hr. After a further 1 hr at room temperature, water was added and the product isolated with ether. The combined ether extracts were washed with saturated salt solution, 5% sodium carbonate solution, water, dried (Na_2SO_4) and evaporated. The oily product was adsorbed from benzene–hexane (1 : 1; 30 cm³) onto neutral alumina (10 g). Elution with benzene–hexane (1 : 1; 150 cm³) afforded 6α-fluoro-Δ⁴-androstene-3,17-dione (XVI) (63 mg), m.p. 212–228°, raised by crystallization from acetone–hexane to 229–231°, $[\alpha]_D$ +185°; λ_{max} 234–236, log ε 4·19.

Anal. Calcd. for $C_{19}H_{25}O_2F \cdot \frac{1}{2}(CH_3)_2CO$: C, 73·9; H, 8·4; F, 5·7. Found: C, 74·3; H, 8·5; F, 5·7.

(b) This was performed by isomerization of compound XII. 6β-Fluoro-Δ⁴-androstene-3,17-dione (XII) (100 mg) in glacial acetic acid (15 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 1 hr and then kept at room temperature for 1 hr. Isolation of the product as in (a) afforded 6α-fluoro-Δ⁴-androstene-3,17-dione (XVI) (50 mg) m.p. 216–218°, raised by crystallization from acetone-hexane to 230–232°, undepressed on admixture with a sample prepared as in (a); $[\alpha]_D$ +190°; λ_{max} 236 mμ, log ε 4·19.

6α-Fluorotestosterone (XIV). (a) A solution of 6α-fluoro-Δ^4-androstene-3,17-dione (XVI) (490 mg) in ether–tetrahydrofuran (1 : 1; 60 cm³) was added to a suspension of lithium aluminum hydride (400 mg) in ether (30 cm³) over a 10 min period. After stirring for a further 15 min at room temperature the excess of reagent was destroyed with ethyl acetate. Hydrochloric acid (2 N, 50 cm³) was then added and the product isolated with ether. The combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated to afford a mixture of alcohols (XV) epimeric at C-3. The total product was dissolved in chloroform (45 cm³) and stirred for 22 hr with manganese dioxide[23*] (4·4 g). Filtration and evaporation of the solvent gave a product (λ_{max} 238 mμ, log ε 3·93), which was adsorbed from benzene onto neutral alumina (30 g). Elution with benzene–ether (80 : 20; 400 cm³) afforded 6α-fluorotestosterone (XIV) m.p. 150–157°, raised by several crystallizations from benzene–hexane to 164–166°, $[\alpha]_D$ +111°, λ_{max} 236–238 mμ, log ε 4·16, $\lambda_{max}^{CHCl_3}$ 3450 cm^{-1}, 1675 cm^{-1}.

Anal. Calcd. for $C_{19}H_{27}O_2F\frac{1}{2}H_2O$: C, 72·3; H, 8·9; F, 6·0. Found: C, 72·5; 72·2; H, 8·9; 8·9. F, 5·7.

(b) Isomerization of 6β-fluorotestosterone was performed as follows: 6β-Fluorotestosterone (XI) (100 mg) in acetic acid (15 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 1 hr and then kept for an additional hour at room temperature. Isolation of the product in the manner described for the conversion of XII to XVI afforded 6α-fluorotestosterone (XIV) (42 mg) m.p. 156–163°, raised by crystallization from benzene–hexane to 163–166°, $[\alpha]_D$ +105°, undepressed on admixture with a sample prepared as in (a).

6β-Fluoro-Δ^4-androstene-3β,17β-diol diacetate (IX). Thionyl chloride (0·2 cm³) was added to a solution of 6β-fluoroandrostane-3β,5α,17β-triol 3,17-diacetate (VII) (500 mg) in pyridine (10 cm³) at 0°, and the mixture kept at that temperature for 5 min. Water was added and the product isolated with ether. The combined ether extracts were washed with 2 N hydrochloric acid, water, dried (Na_2SO_4) and evaporated to afford a product which was adsorbed from benzene–hexane (50 : 50; 50 cm³) onto neutral alumina (25 g). Elution with benzene–hexane (50 : 50; 300 cm³) afforded 6β-fluoro-Δ^4-androstene-3β,17β-diol diacetate (450 mg), m.p. 130–135°, raised by several crystallizations from hexane to 136–138°. $[\alpha]_D$ −42°.

Anal. Calcd. for $C_{23}H_{33}O_4F$: C, 70·4; H, 8·5; F, 4·8. Found: C, 70·9; H, 8·5; F, 4·6.

6β-Fluorotestosterone (XI). A solution of 6β-fluoro-Δ^4-androstene-3β,17β-diol-diacetate (IX) (2·0 g) in ether (200 cm³) was added to a suspension of lithium aluminum hydride (1·0 g) in ether (100 cm³) at 0–5° over 10 min and then stirred for a further 10 min, when the excess of reagent was destroyed with acetone. Saturated sodium sulfate solution (5·0 cm³) and sufficient anhydrous sodium sulfate to give a clear supernatant ether solution was then added. The solution was filtered and the solid residue was extracted several times with chloroform. The combined extracts were evaporated under reduced pressure at 30° and the residue (1·8 g) had no carbonyl absorption in the infrared. A portion of this crude diol (1·6 g) in chloroform (100 cm³) was stirred with manganese dioxide (16 g) for 16 hr at room temperature. Filtration and evaporation of the filtrate afforded a product (λ_{max} 236 mμ, log ε 4·03) which

* The manganese dioxide was prepared according to the directions of O. Mancera *et al.*

[23] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 2189 (1953).

was adsorbed from benzene (100 cm³) onto neutral alumina (100 g). Elution with benzene–ether (80 : 20; 50 cm³) afforded 6β-fluorotestosterone (XI) (1·08 g), m.p. 160–164°, raised by several crystallizations from benzene–hexane to 169–171°, $[\alpha]_D$ ±0°, λ_{max} 234 mμ, log ε 4·09, $\lambda_{max}^{CHCl_3}$ 3550, 1680 and 1625 cm⁻1.

Anal. Calcd. for $C_{19}H_{23}O_2F$: C, 74·5; H, 8·9; Found: C, 74·1; H, 8·9.

6β-Fluoro-Δ⁴-androstene-3,20-dione (XII). A solution of 6β-fluoro-Δ⁴-androstene-3β,17β-diol diacetate (IX) (2·0 g) was hydrolyzed with lithium aluminum hydride as described in the previous experiment. The crude diol in acetone (50 cm³) was oxidized with 8 N chromic acid in the usual way. Isolation with ether afforded a product (1·5 g) m.p. 101–115°, which was adsorbed from benzene–hexane (1 : 1; 100 cm³) onto alumina (80 g). Elution with benzene (900 cm³) afforded 6β-fluoro-Δ⁴-androstene-3,17-dione (XII) (1·1 g) m.p. 130–137°, raised by crystallization from acetone–hexane to 136–138°, $[\alpha]_D$ +78°, λ_{max} 234, log ε 4·10, $\lambda_{max}^{CHCl_3}$ 1730 cm⁻¹ and 1675 cm⁻¹.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 75·0; H, 8·3; F, 6·2. Found: C, 75·3; H, 8·3; F, 5·5.

5α,6α-Oxidopregnane-3β-ol-20-one 3-acetate (XVIII). A solution of per monophtalic acid[24] (15 g) in ether (500 cm³) was added during 20 min to a solution of pregnenolone acetate (XVII) in chloroform (800 cm³) at −60° to −70° (acetone–CO_2 bath). After keeping at −60° for a further 2 hr the mixture was kept at 0–5° for 16 hr. Chloroform (200 cm³) was added and the organic phase was washed with 5% sodium carbonate solution and water, dried (Na_2SO_4) and evaporated. The residue crystallized from methanol to afford 5α, 6α-oxido-pregnane-3β-ol-20-one acetate (XVIII) (13·5 g) m.p. 158–160°, raised by crystallization from methanol to 166–168°, $[\alpha]_D$ +11°. Ehrenstein and Decker[25] report m.p. 163–165° but give no $[\alpha]_D$ measurement. Urushibora *et al.*[26] report m.p. 165–166°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73·8; H, 9·1. Found: C, 73·8; H, 9·0.

6β-Fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX). Boron trifluoride etherate (8·7 cm³) was added to a solution of 5α,6α-oxidopregnane-3β-ol-20-one 3-acetate (8·7 g) in anhydrous ether–benzene (1 : 1; 700 cm³). After keeping at room temperature for 6 hr the solution was washed with 5% sodium bicarbonate solution, water, and then dried (Na_2SO_4) and evaporated. A solution of the product in benzene–hexane (1 : 1; 200 cm³) was adsorbed onto alumina (400 g). Elution with benzene (1·0 l.) afforded 5α,6α-oxidopregnane-3β-ol-20-one-3-acetate (2·4 g) identical with starting material. Further elution with benzene–ether (80 : 20; 1·7 l.) afforded 6β-fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX) (3·6 g), m.p. 218–220°, raised by several crystallizations to 223–224°, $[\alpha]_D$ +42°.

Anal. Calcd. for $C_{23}H_{35}O_4F$: C, 70·5; H, 8·9; F, 4·6. Found: C, 70·8; H, 8·9; F, 4·8.

6β-Fluoropregnane-3β,5α,20β-triol (XXII). A solution of 6β-fluoropregnane-3β, 5α-diol-20-one 3-monoacetate (XIX) (3·1 g) in dry ether (850 cm³) was added with stirring during 20 min to a suspension of lithium aluminum hydride (3·0 g) in ether (750 cm³) at 10°. After stirring at room temperature for a further 15 min the excess of reagent was destroyed with ethyl acetate. Saturated sodium sulfate solution

[24] *Organic Synthesis* (Coll. Vol. 3) p. 619. Wiley, New York (1955).
[25] M. Ehrenstein and M. T. Decker, *J. Org. Chem.* **5**, 544 (1940).
[26] Y. Urushibora, M. Chuman and S. Wada, *Bull. Chem. Soc. Japan* **24**, 83 (1951).

(10 cm³) was then added and sufficient anhydrous sodium sulfate to give a clear supernatant ether solution, which was filtered and the solid residue was extracted several times with chloroform. The combined extracts were evaporated to afford crude 6β-fluoropregnane-3β,5α,20β-triol (XXII) (2·6 g), m.p. 218–220°, raised by crystallization from acetone–hexane to 228–230°, $[\alpha]_D \pm 0°$ (dioxan).

Anal. Calcd. $C_{21}H_{35}O_3F$: C, 71·1; H, 9·4; F, 5·3. Found: C, 71·4; H, 9·7; F, 5·1.

6β-Fluoropregnane-5α-ol-3,20-dione (XXV). A solution of 6β-fluoropregnane-3β, 5α,20β-triol (XXII) (3 g) in acetone (200 cm³) at 0–5° was treated with an excess of 8 N chromic acid in the usual way. Addition of water and filtration afforded 6β-fluoropregnane-5α-ol-3,20-dione (XXV) (2·4 g), m.p. 245–247°, raised by one crystallization from aqueous pyridine to 279–281°, $[\alpha]_D +78°$ (pyridine).

Anal. Calcd. for $C_{21}H_{31}O_3F$: C, 71·9; H, 8·9; F, 5·4. Found: C, 71·8; H, 9·1; F, 4·9.

6α-Fluoroprogesterone (XXIV). A suspension of 6β-fluoropregnane-5α-ol-3, 20-dione (XXV) (800 mg) in acetic acid (80 cm³) at 15° was treated with a steady stream of dry hydrogen chloride for 2 hr and then kept at room temperature for 16 hr. Water was added and the product isolated with ether. After washing the combined ether extracts with 5% sodium carbonate solution, water, and drying over sodium sulfate, evaporation afforded a product which was adsorbed from benzene–hexane (50 : 50; 100 cm³) onto alumina (40 g). Elution with benzene–ether (90 : 10; 400 cm³) gave 6α-fluoroprogesterone (XXIV) (260 mg), m.p. 123–133°, raised by crystallization from acetone–hexane to 146–148°, $[\alpha]_D +191°$, λ_{max} 236, log ε 4.19.

Anal. Calcd. for $C_{21}H_{29}O_2F$: C, 75·9; H, 8·8; F, 5·7. Found: C, 75·8; H, 9·0; F, 5·8.

Dehydration of 6β-fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX). Thionyl chloride (0·1 cm³) was added to a solution of XIX (250 mg) in pyridine (5 cm³ at 0°). After 5 min at 0°, water was added and the product isolated with ether. The combined ether extracts were washed with 2 N hydrochloric acid, water, dried (Na_2SO_4) and evaporated to afford a product (200 mg), m.p. 90–94°, raised by crystallization from hexane to 94–97°, $[\alpha]_D +33°$.

Anal. Calcd. for $C_{23}H_{33}O_3F$: C, 73·5; H, 8·8. Found: C, 73·7; H, 8·8.

Hydrolysis (3β-acetate) and reduction (20 ketone) of the dehydration product. The total dehydration product (from the previous experiment) in ether (10 cm³) was added dropwise over 5 min to a stirred suspension of lithium aluminum hydride (200 mg) in ether (10 cm³) at 15°. After stirring for a further 15 min the excess of reagent was destroyed with acetone and the product isolated by the sodium sulfate method (as described above), to afford a non-crystalline product having no carbonyl absorption in the infrared.

Oxidation of the product from the previous experiment. (a) With manganese dioxide. The crude product (50 mg) in chloroform (5 cm³) was stirred with manganese dioxide (500 mg) for 24 hr. Filtration and evaporation of the solvent gave a product λ_{max} 236 mμ, log ε 3·71.

(b) With 8 N chromic acid in sulfuric acid. Crude product (100 mg) in acetone (10 cm³) at 0° was treated with an excess of 8 N chromic acid under nitrogen at 0°. After 3 min water was added and filtration afforded a product (92 mg) m.p. 156–160°, λ_{max} 236 mμ, log ε 3·80, raised by one drop of dilute alkali to 4·10.

6β-Fluoroprogesterone (XXVI). (a) 6β-Fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX) (2·2 g) was treated with thionyl chloride in pyridine as described above. The total dehydration product in ether (100 cm³) was then added dropwise over 10 min to a stirred suspension of lithium aluminum hydride (2·0 g) in ether (100 cm³) at 15°. After stirring for a further 15 min at room temperature the excess of reagent was destroyed with acetone and the product isolated by the sodium sulfate method to afford a non-crystalline product having no carbonyl absorption in the infrared. The total product in chloroform (100 cm³) was stirred for 16 hr with manganese dioxide (20 g). Filtration afforded a product λ_{max} 236 mμ, log ε 3·78, indicating that approximately 47 per cent of XXIII was present in this mixture. A solution of the total oxidation product in benzene (100 cm³) was adsorbed onto alumina (100 g). Elution with benzene–ether gave a product (850 mg) m.p. 150–155°, λ_{max} 236 mμ, log ε 4·07. Without further purification a solution of this product in acetone (50 cm³) at 0–5° was treated with an excess of 8 N chromic acid in the usual way. Addition of water and filtration gave 6β-fluoroprogesterone (XXVI) (640 mg), m.p. 156–159°, raised by several crystallizations from benzene–hexane to 159–161° $[\alpha]_D$ +104°. λ_{max} 234–236 mμ, log ε 4·12.

Anal. Calcd. for $C_{21}H_{29}O_2F$: C, 75·9; H, 8·8; F, 5·7. Found: C, 75·7; H, 8·8; F, 5·6.

(b) 6β-Fluoropregnane-5α-ol-3,20-dione (XXV) (1·5 g) was suspended in methanol (100 cm³) containing potassium hydroxide (0·25 g) and heated under reflux under nitrogen for 60 min, when a clear solution resulted. After acidification with acetic acid and concentration of the solution to 15 cm³, water was added. Filtration of the precipitate gave a product (1·1 g), m.p. 125–130°, $[\alpha]_D$ +133°. Chromatography over alumina and crystallization from benzene–hexane afforded 6β-fluoroprogesterone (XXVI) (300 mg), m.p. 156–158°, $[\alpha]_D$ +110°, undepressed on admixture with a sample prepared in method (a) and markedly depressed (119–124°) on admixture with 6α-fluoroprogesterone (XXIV).

Isomerization of 6β-fluoroprogesterone (XXVI). 6β-Fluoroprogesterone (100 mg) in acetic acid (15 cm³) at 15° was treated with a steady stream of dry hydrogen chloride for 90 min. After keeping at room temperature for an additional 90 min, water was added. Isolation with ether afforded 6α-fluoroprogesterone (XXIV), m.p. 138–142°, $[\alpha]_D$ +188°, raised by crystallization from hexane–ether to 143–145°, undepressed on admixture with an authentic sample.

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STEROIDS—XCIV*

SYNTHESIS OF 2-METHYL- AND 1,2-DIMETHYL-ESTROGENS

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Abstract—2-Methyl-and 1,2-dimethyl-estrogens have been derived from 2-methyltestosterone via the $\Delta^{1,4}$ and ^{1,4,6} compounds. Ultraviolet, rotatory and biological influences of alkyl substituents in the phenolic steroids series are discussed.

IN continuation of our program to determine the effect of alkyl substitution on steroidal hormone biological activity,[1,2] we have prepared a number of 2-methyl and 1,2-dimethyl substituted derivatives of estrone and of estradiol. The only known derivatives of this type are the 1-methyl derivatives of estrone first prepared by Djerassi *et al.*[3] by "dienone-phenol rearrangement" of a $\Delta^{1,4,6}$-trien-3-one and 1,4-dimethylestradiol recently reported by Sondheimer and Mazur[4] by "dienone-phenol rearrangement" of 4-methyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one. A compound of the natural estrogen structure but partly inactivated biologically (i.e., a non-estrogenic estrogen) by the presence of additional alkyl groups could possibly possess a number of important applications.

Our starting material, 2α-methyltestosterone (I),[1] on treatment with selenium dioxide,[5,6,7,8] preferably in *tert.*-butanol,[6,7] was readily converted to the $\Delta^{1,4}$-dienone (II) in over 80 per cent yield. While comparable yields with selenium dioxide have been reported[6] in dehydrogenations in the cortical hormone series, the yields in general in the testosterone and substituted testosterone series are very low[4,5,6,7] (ca. 35 per cent or less), owing primarily to formation of a selenium complex of the derived $\Delta^{1,4}$-dienone. Such a complex has been reported in the selenium dioxide dehydrogenation of testosterone,[8] 17α-methyltestosterone[6] and 4-methyltestosterone.[4] The exceptionally high yield in the case of the C-2 methyl-substituted (II) and the absence of selenium complexes prompts us to postulate that the selenium–dienone compounds formed in the above-mentioned cases have at least one linkage at C-2.

The dienone (II), after chromic acid oxidation to 2-methyl-$\Delta^{1,4}$-androstadien-3, 17-dione (VII), was identical with the product obtained by dibromination of

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2α-methylandrostane-3,17-dione (VI) followed by collidine dehydrobromination of the 2,4-dibromo compound. Pyrolysis of (II) in mineral oil at 600° as described previously [9,10] gave 2-methylestradiol (IIIa). 2-Methylestrone (IVa) was readily prepared by Schotten–Baumann benzoylation of (IIIa), chromic acid oxidation of the resultant 3-monobenzoate (IIIb) and alkaline hydrolysis.

It has been previously shown[11] that Δ^4-3-oxosteroids may be dibrominated at C-2 and C-6 in ether–acetic acid solution and that the subsequent $\Delta^{1,4,6}$-trienones derived by dehydrobromination readily undergo acid-catalyzed "dienone–phenol rearrangement" in acetic anhydride solution to give the 3-acetate of the 1-methyl-Δ^6-dehydroestrogens. Ether–acetic acid dibromination of 2α-methyltestosterone did not proceed smoothly, but the crystalline 2,6-dibromide was readily obtained by similar bromination of the corresponding 17-ketone, 2α-methyl-Δ^4-androstene-3,17-dione (VIII). The intermediate 2,6-dibromo compound (IX) probably possesses the 6β-bromo (axial) configuration in view of the high position of the ultraviolet maximum[12] (251 mμ; log ε 4·11). Dehydrobromination of (IX) in boiling collidine gave the desired $\Delta^{1,4,6}$-trienone (X). Under milder dehydrobromination conditions it was possible to stop the reaction at the 6-bromo-$\Delta^{1,4}$-dienone (XV) stage (λ_{max} 246 mμ; log ε 4·20), thereby establishing that the order of elimination of the halogens is reversed* in the presence of a 2-methyl group, a not surprising finding, since the 2-bromine is a tertiary bromide in this case.

The trienone (XI) smoothly underwent rearrangement and aromatization in hot acetic anhydride–toluene-*p*-sulfonic acid solution to yield 1,2-dimethyl-Δ^6-dehyrdoestrone 3-acetate (XIb). Catalytic hydrogenation of this 6-dehydro compound followed by alkaline hydrolysis furnished 1,2-dimethylestrone (XII), while sodium borohydride reduction of (XI) and (XII), respectively, gave the estradiol derivatives 1,2-dimethyl-Δ^6-dehydroestradiol (XIII) and 1,2-dimethyl-estradiol (XIV).

Inspection of molecular-rotation differences (Table 1) reveals that, as one might expect, the contribution of a planar 2-methyl group is insignificant (+5 to +126). On the other hand, the 1-methylestrogens exhibit a somewhat greater positive molecular rotation increment varying from +104 to +271, this shift very likely being due to a minor interaction between the C-1 methyl and the C-11 methylene group of the type already noted in certain 1-methyl-19-norsteroids.[13]

It may be seen from Table 1 that the ultraviolet bathochromic shift attributable to the C-2 methyl group is very slight, varying from 1 to 5 mμ in the different examples. The shift due to a C-1 methyl is slightly greater (+3 to +7 mμ,) although it is of interest to note that the 306 mμ maximum in the Δ^6-dehydroestrogens is essentially unaltered by C-1 methyl substitution or C-1 and C-2 dimethyl substitution.

Biologically† it may be stated as a first approximation that an individual methyl group at C-1 or C-2, as in 1-methylestrone or 2-methylestrone, decreases estrogenic

* Unpublished observation : 2,6-dibromo-Δ^4-androstene-3,17-dione has been dehydrobrominated stepwise in these laboratories, thereby establishing that the 6-bromo atom is eliminated first.

† Bioassays by Dr. R. I. Dorfman, The Worcester Foundation, Shrewsbury, Mass.

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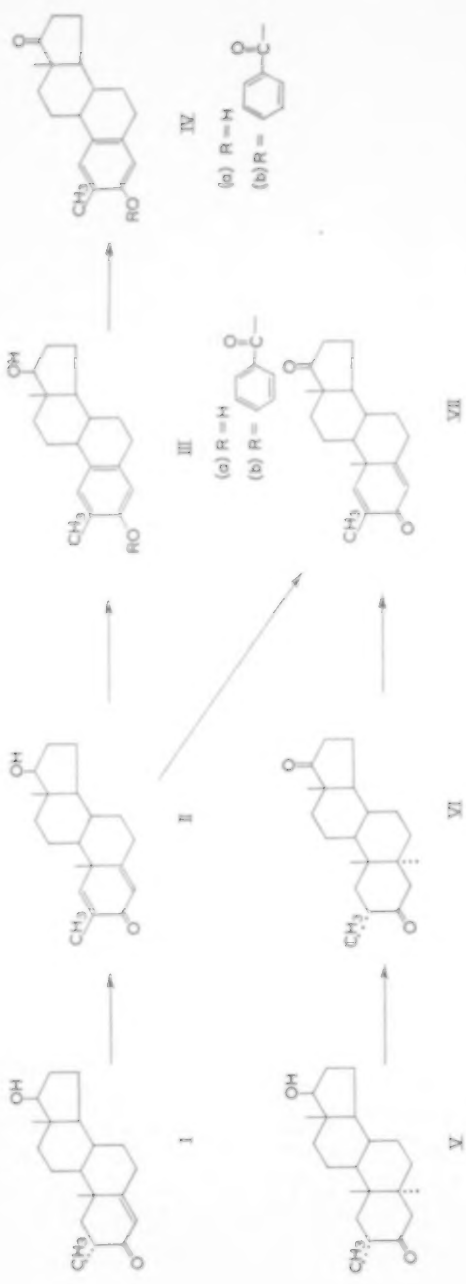

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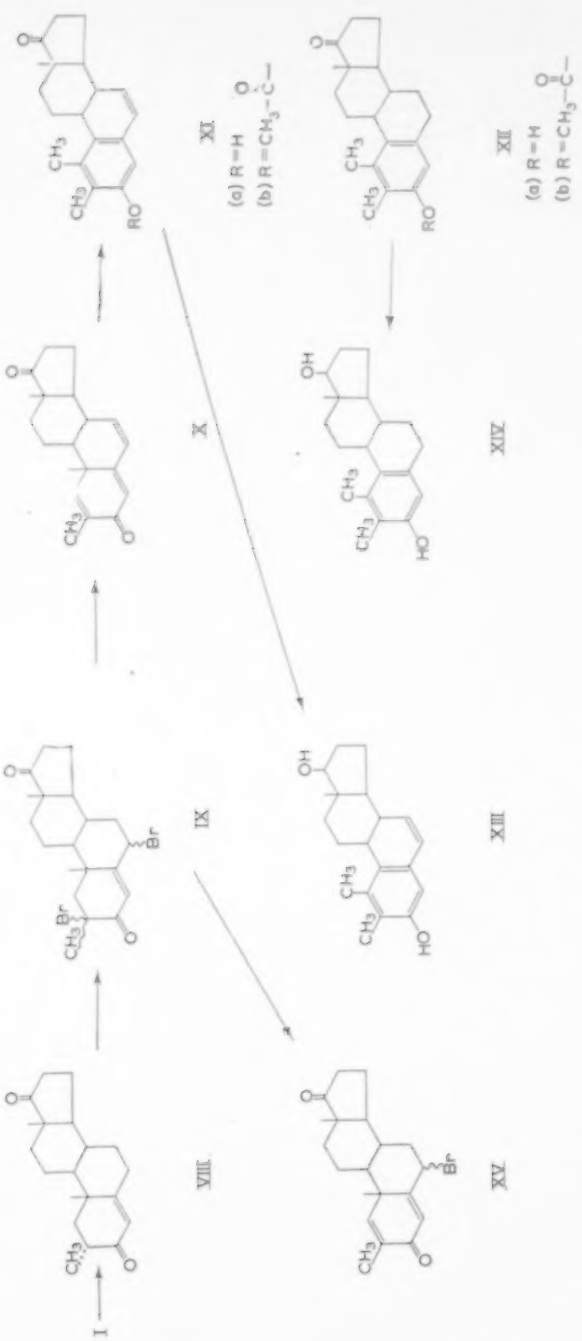
I
VIII
IX
X
XI
(a) R=H
(b) R=CH3-C(=O)-
XII
(a) R=H
(b) R=CH3-C(=O)-
XIII
XIV
XV

TABLE 1. OPTICAL DATA FOR SUBSTITUTED ESTRONES AND ESTRADIOLS

Compound	$[\alpha]_D$ (dioxane)*	$[M]_D$	$\Delta[M]_D$		λ_{max} in alcohol	log ε*
			1-Methyl	2-Methyl		
Estrone	+163°	+460			280	3·37
1-Methylestrone	+247°	+731	+271		287	3·23
2-Methylestrone	+198°	+586		+126	283	3·41
1,2-Dimethylestrone	+258°	+800		+69	288	3·36
6-Dehydroestrone	−124°	−347			221, 262, 306	4·49, 3·95, 3·40
1-Methyl-6-dehydroestrone	−77°	−226	+121		228, 267, 276, 304	4·49, 3·92, 3·82 3·29
1,2-Dimethyl-6-dehydroestrone	−44°	−136		+90	231, 272, 306	4·45, 3·94, 3·38
Estradiol	+80°	+227			280	3·33
1-Methylestradiol	+146°	+435	+208		284	3·28
2-Methylestradiol	+78°	+232		+5	284	3·38
1,2-Dimethylestradiol	+149°	+465		+30	288	3·25
6-Dehydroestradiol	−169°	−477			222, 263, 306	4·50, 3·98, 3·52
1-Methyl-6-dehydroestradiol	−126°	−373	+104		227, 266, 276, 305	4·57, 3·95, 3·74 3·20
1,2-Dimethyl-6-dehydroestradiol	−110°	−328		+40	230, 271, 307	4·49, 3·99, 3·41

* Constants determined in these laboratories.

activity by a factor of up to 200*. The activity decrease for two methyl groups is not completely cumulative, but 1,2-dimethylestrone (XII) and 1,2-dimethyl-Δ^6-dehydroestrone (XI) exhibit less than 1/2000 the uterotrophic activity of estrone in the mouse assay. Despite their low estrogenic activity these two compounds are rather potent anti-androgens as determined by their antagonism to testosterone in the chick comb assay.†

EXPERIMENTAL‡

2-*Methyl*-$\Delta^{1,4}$-*androstadien*-17β-*ol*-3-*one* (*II*)

A solution of 2α-methyltestosterone (I) (2·2 g) in 75 ml of *tert.*-butanol was treated with 2·2 g of selenium dioxide and 2 ml of acetic acid and the mixture was boiled in a nitrogen atmosphere for 72 hr. The cooled suspension after dilution with ethyl acetate was filtered through Celite and concentrated to dryness *in vacuo*, and the residue was treated with water and finally extracted with ethyl acetate. The ethyl

* Considerable variation has been encountered in the assay of the 1-methyl estrogens (see Djerassi *et al.*[3]) particularly in the case of the diesters of 1-methylestradiol, the activity varying with the particular dosage and assay utilized.

† Bioassay by Dr. R. I. Dorfman. The Worcester Foundation, Shrewsbury, Mass.

‡ Melting points are uncorrected. Rotations were determined at 20° and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srita. Ma. Luisa Franco for technical assistance and to Sr. E. Avila for rotation and ultraviolet spectral data.

acetate solution was washed successively with dilute sodium carbonate solution, cold ammonium sulfide, cold ammonia solution water, dilute hydrochloric acid and water. Concentration of the dried solution and trituration with ether furnished 1·5 g of *dienone* (II), m.p. 203–209°. Chromatography of the mother liquors on neutral alumina gave an additional 0·25 g of material, m.p. 209–210°, for an overall yield of 80 per cent. The analytical specimen, from ether, exhibited m.p. 211–212°; $[\alpha]_D$ +6° (chloroform); λ_{max} 248 mμ; log ε 4·23. *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·39. Found: C, 79·90; H, 9·27.

2-*Methylestradiol* (IIIa)

Δ^1-Dehydrotestosterone (II) was pyrolyzed by passing a solution of 3 g of compound in 1·5 l. of mineral oil through a heated (600°) Pyrex-glass tube packed with glass-beads. The cooled mineral-oil solution was diluted with hexane and the phenolic material was separated by extraction with 5% sodium hydroxide solution. Acidification gave crude (IIIa), which was purified by chromatography on 80 g of silica gel. Crystallization of the benzene–ether (9 + 1) fractions from ether–hexane gave 0·5 g of 2-*methylestradiol* (IIIa), m.p. 180–182°. The pure product from ether recrystallization (silky needles) melted at 185–186°; $[\alpha]_D$ +78° (dioxan), λ_{max} 284 mμ; log ε 3·38. *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79·68; H, 9·15; Found: C, 79·98; H, 9·13.

2-*Methylestradiol* 3-*monobenzoate* (IIIb)

Treatment of an aqueous sodium hydroxide solution of the phenol (IIIa) with benzoyl chloride (Schotten–Baumann technique) and crystallization from ether of the precipitate thus formed gave the *benzoate* (IIIb), m.p. 187–190°; λ_{max} 226, 270 mμ; log ε 4·37, 3·58. *Anal.* Calcd. for $C_{26}H_{30}O_3$; C, 79·97; H, 7·74; O, 12·29. Found C, 79·56; H, 7·83; O, 12·53.

2-*Methylestrone benzoate* (IVb)

Chromic acid (0·25) g in 2·5 ml of glacial acetic acid was added to a solution of 0·125 g of (IIIb) in 5 ml of acetic acid and the solution (slow deposition of crystals) was set aside for 1 hr at 25°. Water was added, and the crystalline precipitate filtered off, washed, air-dried and recrystallized from ether, to yield plates (0·08 g), m.p. 212°; $[\alpha]_D$ +183° (dioxan); λ_{max} 226, 270 mμ; log ε 4·36, 3·54. *Anal.* Calcd. for $C_{26}H_{28}O_3$: C, 80·38; H, 7·26; O, 12·36. Found: C, 80·15; H, 7·58; O, 12·65.

2-*Methylestrone* (IVa)

The benzoate (IVb) (0·1 g) was added to 5 ml of 1% methanolic potassium hydroxide, and the solution was boiled for 1 hr neutralized with acetic acid, concentrated and treated with salt solution. The precipitate thus obtained was taken up in ether, the solution was decolorized with charcoal and pure 2-*methylesterone* (0·05 g) was obtained by ether–hexane crystallization, m.p. 221–225°; $[\alpha]_D$ +198° (dioxan); λ_{max} 283 mμ; log ε 3·41. *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80·24; H, 8·51. Found: C, 80·06; H, 8·49.

2α-*Methylandrostane*-3,17-*dione* (VI)

2α-Methylandrostan-17β-ol-3-one (V)[1] (3 g) in 40 ml of glacial acetic acid was treated over a 10 min period with a solution of 1·5 g of chromic acid in 10 ml of water

and 40 ml of acetic acid. The oxidation was allowed to proceed for 1 hr in addition at 25°, and the solution was then poured into water and the crystalline precipitate was filtered off, washed and dried. Recrystallization from ether–hexane gave 2·3 g (77 per cent) of (VI), m.p. 148–149°. The analytical sample, from ether, melted at 152–153°; $[\alpha]_D$ +110° (chloroform). *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79·42; H: 10·00. Found C, 79·28, H, 9·95.

2-*Methyl*-$\Delta^{1,4}$-*androstadiene*-3,17-*dione* (VII) *from* (VI)

The dione (VI) (1·0 g) dissolved in 30 ml of glacial acetic acid was dibrominated at 18° by the slow addition of 15·2 ml of a solution of bromine in acetic acid (0·07 g/ml) (2·0 equivalents). Bromine uptake was rapid, but the solution was set aside for 1 hr and then poured into 300 ml of ice–water. The crude 2,4-dibromo compound was filtered off, thoroughly washed with water and dried *in vacuo*; the yield was 1·25 g of product, m.p. 140–145° (dec.). Without further purification the crude bromo compound was dehydrobrominated by being heated with 20 ml of boiling γ-collidine for 4 hr with exclusion of moisture. The mixture was cooled, diluted with ether and the precipitated amine hydrobromide (0·87 g) was removed and washed with ether. The filtrate was washed with excess of 5% hydrochloric acid, water and sodium bicarbonate solution and was then dried and evaporated. The residue was purified by chromatography on 20 g of neutral alumina, the benzene–ether (2 + 1) fractions yielding 0·56 g of (VII), m.p. 183–188°. Analytical sample from ether, m.p. 198–200°; $[\alpha]_D$ +100° (chloroform); λ_{max} 247 mμ; log ε 4·20. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78. Found: C, 80·33; H, 8·75.

(VII) *from* (II)

Chromic acid oxidation (as described in the preparation of (VI)) of 1 g of (II) gave 0·8 g of 2-methyl-$\Delta^{1,4}$-androstadiene-3,17-dione (VII), m.p. 198–200°, the product being identical in all respects with the dienone obtained by bromination and dehydrobromination of 2α-methylandrostane-3,17-dione (VI).

2α-*Methyl*-Δ^4-*androstene*-3,17-*dione* (VIII)

To a solution of 10 g of 2α-methyltestosterone (I) in 100 ml of glacial acetic acid was added over a 10 min period a solution of 5 g of chromic acid in 25 ml of water and 150 ml of acetic acid. After being set aside at room temperature for 1 hr the mixture was poured into water and the precipitate was collected, washed well with water and dried, to yield 8·6 g of (VIII), m.p. 155–159°. A sample further purified by ether crystallization showed m.p. 159–160°; $[\alpha]_D$ +190° (chloroform); λ_{max} 242 mμ; log ε 4·22. *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·36. Found C, 80·10; H, 9·43.

2,6-*Dibromo*-2-*methyl*-Δ^4-*androstene*-3,17-*dione* (IX)

2α-Methyl-Δ^4-androstene-3,17-dione (VIII) (10 g) was dissolved in 500 ml of anhydrous ether and the solution was cooled to 0°. With agitation and exclusion of moisture, while the temperature was maintained at 0° with an ice–salt bath, a solution of 12 g of bromine (2·0 equivalents) in 20 ml of glacial acetic acid was added dropwise. A slight induction period was noted, but thereafter bromine uptake was smooth and rapid. The reaction mixture was then allowed to come to room temperature, water (200 ml) was added and the ether was removed by distillation *in vacuo* at 25°. The

resultant precipitate was filtered off, washed with water and finally with 5 ml of cold methanol, to yield 10·6 g (69 per cent) of crude 2,6-*dibromo compound*, m.p. 115–120° (dec.). This material was satisfactory for the subsequent step. The pure compound was prepared by recrystallization from methanol, m.p. 128–132° (dec.); $[\alpha]_D$ +49° (chloroform); λ_{max} 251 mμ; log ε 4·11. *Anal.* Calcd. for $C_{20}H_{26}O_2Br_2$: C, 52·42; H, 5·72; Br, 34·88. Found: C, 52·42; H, 5·75; Br, 32·20.

2-*Methyl*-$\Delta^{1,4,6}$-*androstatriene*-3,17-*dione* (X)

A solution of 6 g of crude dibromo compound (IX) in 25 ml of γ-collidine was boiled under reflux for 1 hr with exclusion of moisture. It was then cooled, diluted with ethyl acetate and the collidine hydrobromide (4·8 g) was filtered off and washed with ethyl acetate. The filtrate was washed with dilute hydrochloric acid and water, dried and concentrated, to leave 3·5 g of a semi-crystalline residue. This material was chromatographed on 150 g of neutral alumina, the benzene–ether extracts yielding, after recrystallization from ethyl acetate–ether, 2.1 g (54 per cent) of *trienone* (X), m.p. 197·5–199°; $[\alpha]_D$ +60° (chloroform); λ_{max} 266, 301 mμ; log ε 4·04, 3·98. *Anal.* Calcd. for $C_{20}H_{24}O_2$; C, 81·04; H, 8·16. Found: C, 80·82; H, 8·17.

6-*Bromo*-2-*methyl*-$\Delta^{1,4}$-*androstadiene*-3,17-*dione* (XV)

A solution of 1·1 g of 2,6-dibromo compound (IX) in 7 ml of γ-collidine–xylene (1 + 1) was boiled under reflux for 20 min. Ethyl acetate was added to the cooled solution, the separated collidine hydrobromide (0·56 g) was filtered off, and the filtrate was washed with dilute hydrochloric acid and water, and then evaporated to dryness *in vacuo*. Crystallization of the residue from methanol gave 0·28 g of 6-*bromo*-2-*methyl*-$\Delta^{1,4}$-*androstadiene*-3,17-*dione* (XV), m.p. 211–213° (dec.). Recrystallization from the same solvent gave the analytical sample as shiny plates, m.p. 216–218°; $[\alpha]_D$ +32° (chloroform); λ_{max} 246 mμ; log ε 4·20. *Anal.* Calcd. for $C_{20}H_{25}O_2Br$: C, 63·66; H, 6·68; Br, 21·18. Found: C, 62·96; H, 6·76; Br. 21·20.

1,2-*Dimethyl*-Δ^6-*dehydroestrone acetate* (XIb)

A mixture of 5 g of trienone (X), 100 ml of acetic anhydride and 2 g of toluene-*p*-sulfonic acid hydrate was heated at 90° for 5 hr. The cooled solution was poured into ice–water and stirred until the excess of anhydride had hydrolyzed, and the crystalline precipitate was filtered off, thoroughly washed with water and air-dried. Recrystallization from methanol gave 4·34 g per cent (76 per cent) of the *acetate* (XIb), m.p. 178–180°. The analytical specimen from the same solvent melted at 180–181°; $[\alpha]_D$ −53° (dioxan); λ_{max} 225, λ_{max} 225, 266 mμ; log ε 4·45, 3·11 266 mμ; log ε 4·45 3·11, *Anal.* Calcd. for $C_{22}H_{26}O_3$: C, 78·07; H, 7·74. Found: C, 77·80; H, 7·70.

1,2-*Dimethyl*-Δ^6-*dehydroestrone* (XI)a

The acetate (XIb) (1·7 g) was added to 400 ml of 1% methanolic potassium hydroxide and the mixture was boiled for 30 min in a nitrogen atmosphere. Acetic acid (10 ml) was added, the solution was concentrated to ca. 30 ml and salt and water were added. The crude precipitate thus formed (1·6 g) was recrystallized from ethyl acetate and then from methanol to yield 1·1 g (74 per cent) of pure 1,2-*dimethyl*-Δ^6-*dehydroestrone* (XIa), m.p. 254–255°; $[\alpha]_D$ −44° (dioxan); λ_{max} 231, 272, 306 mμ;

log ε 4·45, 3·92, 3·38. *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81·04; H, 8·16. Found: C, 81·29; H, 8·17.

1,2-*Dimethylestrone acetate* (XIIb)

The dehydroestrone acetate (XIa) (1·13) g was added to 50 ml of ethyl acetate containing 50 mg of prehydrogenated 10% palladium–carbon catalyst and the compound was hydrogenated at atmospheric pressure (570 mm) and 25°. In 1 hr 122 ml (1·1 moles) of hydrogen were adsorbed; the catalyst was filtered off and the solution was evaporated to dryness. The crude product (1·1 g), m.p. 204–206°, was crystallized from methanol, whereby the melting point rose to 210–211°; $[\alpha]_D$ +223° (dioxan); λ_{max} 272, 280 mμ; log ε 2·73, 2·73. *Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29. Found: C, 77·64; H, 8·32.

1,2-*Dimethylestrone* (XIIa)

Hydrolysis of 0·5 g of acetate (XIIb) as described for the preparation of (XIa) gave 0·41 g (94 per cent) of 1,2-*dimethylestrone* (XIIa), m.p. 267–275°. The analytical sample, from methanol, exhibited m.p. 274–275°; $[\alpha]_D$ +257° (chloroform), 270° (dioxan); λ_{max} 288 mμ; log ε 3·36. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78. Found: C, 80·38; H, 8·73.

1,2-*Dimethyl-*Δ^6*-dehydroestradiol* (XIII)

A solution of 0·52 g of 1,2-dimethyl-Δ^6-dehydroestrone acetate (XIb) in 100 ml of methanol was treated with 0·7 g of sodium borohydride dissolved in 2 ml of water. The solution was boiled for 10 min and then set aside at room temperature for 1 hr. Acetic acid (5 ml) was added, and the solution was partly concentrated *in vacuo*, cooled, poured into ice–water and extracted with ethyl acetate. Evaporation to dryness of the ethyl acetate solution gave 0·43 g (94 per cent) of (XIII), m.p. 229–231.° The analytical sample was obtained by recrystallization from methanol and it showed m.p. 231–232°; $[\alpha]_D$ −110°; λ_{max} 230, 270–272, 306–308 mμ; log ε 4·49, 3·99, 3·41. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78. Found: C, 80·94; H, 8·85.

1,2-*Dimethylestradiol* (XIV)

A solution of 0·22 g of 1,2-dimethylestrone (XIIa) in 100 ml of methanol was treated with 0·25 g of sodium borohydride in a few millilitres of water and the solution was set aside at room temperature for 16 hr. Acetic acid (2 ml) was added, and the solution was concentrated *in vacuo* to a gummy residue, water was added and the steroid was extracted with ethyl acetate. Evaporation of the extract gave an oil that, on treatment with hexane, was converted to an amorphous powder (XIV), m.p. 120–125°; $[\alpha]_D$ +149° (dioxan); λ_{max} 288 mμ; log ε 3·25. *Anal.* Calcd. for $C_{20}H_{28}O_2 \cdot \frac{1}{2}H_2O$: C, 77·63; H: 9·45. Found: C, 77·15, H, 9·47.

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THE ADDITION OF HYDROCYANIC ACID TO Δ^{16}-PREGNEN-20-ONES

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Abstract—Hydrocyanic acid adds to the 16-double bond of $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate to produce 16α-cyano-Δ^{5}-pregnen-3β-ol-20-one. Similar additions of hydrocyanic acid to Δ^{16}-20-oxo pregnenes are described. By alkaline hydrolysis of the 16α-nitrile group the corresponding acid was obtained, of which several derivatives are described.

THE addition of alcohols,[1,2,3] mercaptans[4] and amines[5] to the 16-double bond of $\Delta^{5,16}$-3β-hydroxypregnadien-20-one (I) has been reported recently. The purpose of this paper is to report the addition of hydrocyanic acid to Δ^{16}-pregnen-20-ones, when a 16-nitrile group is formed. It was found that, by heating a methanolic solution of the ketone (Ia) under reflux with sodium cyanide, there was a smooth addition of hydrocyanic acid. The strongly alkaline medium catalyzes the reaction, simultaneously producing hydrolysis of the 3-acetyl group, to give a good yield of the cyano derivative (IIa). It was proved that the hydrocyanic acid did not react with the 20-oxo group to form a cyanohydrin, because the cyano derivative shows, in the infrared region, bands at 4·5 μ, corresponding to a nitrile, and at 5·9 μ, due to the 20-oxo group. An oxime can also be obtained. The more stable equatorial α-configuration was assigned to the 16-nitrile group by similarity with other additions to this double bond.[2,3]

The Oppenauer oxidation of Δ^{5}-3β-hydroxypregnen-20-one (IIa) yielded 16α-cyanoprogesterone (III).

The addition of hydrocyanic acid to $\Delta^{1,3,5(10),16}$-3-acetoxy-17β-acetylestratetraene (IV)[6] furnished the cyano derivative (Va), while the $\Delta^{5,16}$-3β,21-diacetoxypregnadien-20-one (Ib)[7] yielded the corresponding nitrile, isolated as the 3,21-diacetate (IIc).

The alkaline hydrolysis of the cyano derivative (IIa) produced the Δ^{5}-3β-hydroxy-16α-carboxypregnen-20-one (VIa). The Oppenauer oxidation of its methyl ester (VIb) gave 16α-carbomethoxyprogesterone (VIIb), which by alkaline hydrolysis furnished 16α-carboxyprogesterone (VIIa). This product is produced also by alkaline hydrolysis of 16α-cyanoprogesterone (III).

Hydroxymethylprogesterone (IXa) was prepared for biological tests. This was accomplished by blocking the two keto groups of (VIIb) to form the bisethylenedioxyderivative (VIII), followed by reduction with lithium aluminum hydride and

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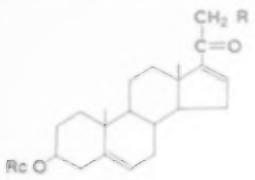
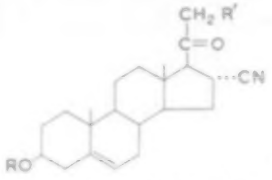
acid hydrolysis of the ketal groupings. The infrared spectrum of hydroxymethylprogesterone (IXa) shows an unusually weak band at 5·9 μ, corresponding to the 20-oxo group. For this reason it is assumed that the above-mentioned product is a mixture of the tautomers (IXa) and (IXb), (IXb) predominating.* This type of hemiketal ring in (IXb) is very similar to that present in aldosterone.[8]

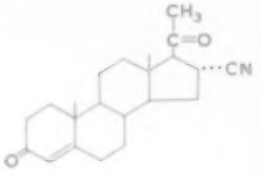
The sodium borohydride reduction of the methyl ester (VIc) yielded the hydroxy derivative (Xa), which on alkaline hydrolysis afforded the free diol (Xb). This product does not form a lactone between the 16α-carboxyl and the 20-hydroxyl groups



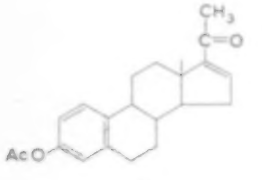
I a, R = H
b, R = OCOCH3



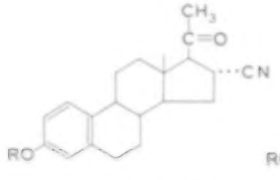
II a, R = H, R' = H
b, R = Ac, R' = H
c, R = Ac, R = OCOCH3



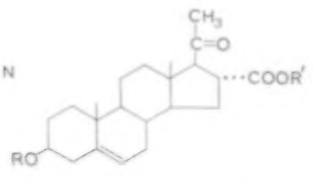
III



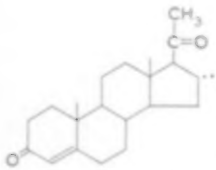
IV



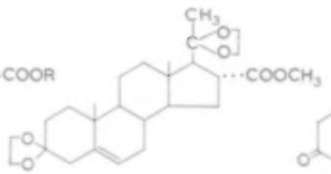
V a, R = H
b, R = Ac



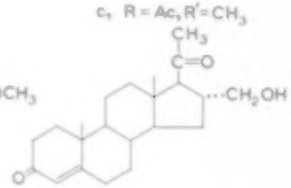
VI a, R = H, R' = H
b, R = H, R' = CH3
c, R = Ac, R' = CH3



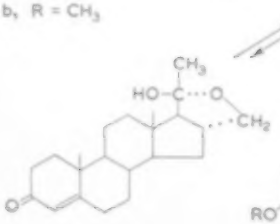
VII a, R = H
b, R = CH3



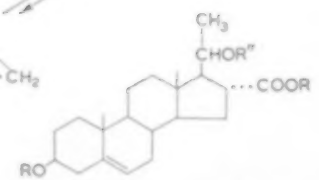
VIII



IX a



IX b



X a, R = Ac, R' = CH3, R'' = H
b, R = H, R' = H, R'' = H
c, R = Ac, R' = H, R'' = Ac

* The optical rotatory dispersion of this mixture (to be published by Dr. Carl Djerassi) substantiates this assumption.

[8] S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. V. Euw, O. Schindler and T. Reichstein, *Experientia* **10**, 132 (1954).

even on treatment with dehydrating agents like acetic anhydride, which produces only the acid diacetate (Xc). This fact proves that the 16-carboxyl and the 20-hydroxyl groups are *trans* to each other and that the reduction with soldium borohydride in this case has produced the β isomer.

The pharmacological activity of the new compounds will be reported elsewhere.

EXPERIMENTAL*

Δ^5-3β-*Hydroxy*-16α-*cyanopregnen*-20-*one* (IIa).

To a solution of 3 g of $\Delta^{5,16}$-3β-acetoxypregnadien-20-one (I) in 80 ml of methanol, 8 g of sodium cyanide were added. The mixture was heated under reflux for 3 hr and then poured into 400 ml of cold water. The precipitate was collected and washed thorougly with water. Crystallization from methanol afforded the *cyano derivative* (IIa) (2·17 g), m.p. 228–232°. The analytical sample was obtained by recrystallizations from acetone–methanol, m.p. 232–234° (thick prisms); $[\alpha]_D$ +14°; λ_{max} 3, 4·5, 5·9 μ. *Anal.* Calcd. for $C_{22}H_{31}O_2N$: C, 77·37; H, 9·15; N, 4·10. Found: C, 77·57; H, 9·22; N, 4·31.

The *acetate* (IIb) (acetic anhydride and pyridine on the steam-bath) showed m.p. 196–198°; $[\alpha]_D$ +16°; λ_{max} 4·5, 5·8, 5·85 μ. *Anal.* Calcd. for $C_{24}H_{33}O_3N$: C, 75·16; H, 8·67; N, 3·65. Found: C, 75·01; H, 8·80; N, 3·55.

The *oxime* (hydroxylamine hydrochloride in pyridine and methanol) showed m.p. 241–243°. *Anal.* Calcd. for $C_{24}H_{34}O_3N_2$ C, 72·33; H, 8·60; N, 7·03. Found: C, 72·03; H, 8·46; N, 6·95.

16α-*Cyanoprogesterone* (III)

The cyano derivative (IIa) (8 g) was dissolved in 250 ml of toluene, 20 ml were distilled off to remove moisture, and 90 ml of *cyclo*hexanone and a solution of 4 g of aluminum tri-*iso*propoxide in 20 ml of toluene were added and the mixture was heated under reflux for 1 hr. The volatile components were then removed by steam-distillation. The semi-crystalline residue was extracted with ether, dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization from acetone–hexane gave prisms, m.p. 216–218° (6·33 g). Further crystallizations from acetone–methanol raised the m.p. to 240–242°; $[\alpha]_D$ +159°; λ_{max} 240 mμ; log ε 4·23; λ_{max} 4·5, 5·9, 6·05 μ. *Anal.* Calcd. for $C_{22}H_{29}O_2N$: C, 77·84; H, 8·61; N, 4·13. Found: C, 78·46; H, 8·40; N, 4·05.

$\Delta^{1,3,5(10)}$-3-*Hydroxy*-16α-*cyano*-17β-*acetylestratriene* (Va)

The phenol (IV) (435 mg) was converted into the *cyano derivative*, as in the previous case. Crystallization from acetone–methanol gave prisms, m.p. 240–243° (230 mg); $[\alpha]_D$ +159°; λ_{max} 280–282 mμ; logε 3·36; λ_{max} 3·05, 4·5, 5·9, 6·2, 6·35 μ. *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77·98; H, 7·79; N, 4·33. Found: C, 77·95; H, 7·83; N, 4·26.

The *acetate* (Vb) showed m.p. 175–176°; $[\alpha]_D$ +150°; λ_{max} 268, 276 mμ; log ε

* The melting points are uncorrected. Rotations were determined in chloroform (unless noted otherwise). The ultraviolet absorption spectra were determined in 95 per cent ethanol solution in a Beckman DK2 spectrophotometer. The infrared spectra were measured on a Perkin–Elmer double-beam spectrophotometer in chloroform solution (unless stated otherwise). The microanalyses were performed by Dr. Franz Pascher, Bonn, Germany.

3·30, 3·22; λ_{max} 4·5, 5·75, 5·9, 6·2, 6·35 μ. *Anal.* Calcd. for $C_{23}H_{27}O_3N$: C, 75·59; H, 7·45; N, 3·83. Found: C, 75·26; H, 7·40; N, 3·71.

Δ^5-3β,21-*Diacetoxy*-16α-*cyanopregnen*-20-*one* (IIc)

A solution of 1·3 g of $\Delta^{5,16}$-3β,21-diacetoxy-16α-cyanopregnadien-20-one (Ib) in 50 ml of ethanol was heated under reflux with 2 g of sodium cyanide for 3 hr. It was then diluted with water and extracted with ether; the ethereal extract was washed thoroughly with water, dried and evaporated to dryness. The solid residue was treated with 4 ml of acetic anhydride and 4 ml of pyridine, heated for 1 hr on the steam-bath and poured into water. The precipitate was extracted with ether, and the ethereal extract was washed with diluted hydrochloric acid, sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness. The *nitrile* (IIc) was crystallized from methanol to yield 170 mg, m.p. 191–194°, which on recrystallization from acetone-methanol showed m.p. 195–197°; $[\alpha]_D$ +10°; λ_{max} 4·5, shoulder at 5·75, 5·8 μ. *Anal.* Calcd. for $C_{26}H_{35}O_5N$: C, 70·71; H, 7·99; N, 3·17. Found: C, 70·56; H, 8·03; N, 3·38.

Δ^5-3β-*Hydroxy*-16α-*carboxypregnen*-20-*one* (VIa).

To a solution of 770 mg of the cyano derivative (IIa) in 50 ml of ethanol a solution of potassium hydroxide (3 g) in 10 ml of water was added. The mixture was heated under reflux for 1 hr and then diluted with cold water, the opalescent solution was acidified with 20% hydrochloric acid and the precipitate was collected and washed with water. Crystallization of the *acid* (VIa) from acetone–ether yielded 470 mg, m.p. 217–219°. Further recrystallizations from acetone–ether raised the m.p. to 233–235°; $[\alpha]_D$ −115°; λ_{max} 3, 5·9 μ. *Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73·30; H, 8·95. Found: C, 73·00; H, 9·03.

Δ^5-3β-*Hydroxy*-16α-*carbomethoxypregnen*-20-*one* (VIb)

An ethereal solution of diazomethane (120 ml) (prepared with 4 g of *N*-nitroso-methylurea) was poured dropwise into the acid (Xa) (1·3 g) dissolved in 30 ml of methanol. The solution was left at room temperature overnight. A few drops of acetic acid were added to destroy the excess of diazomethane, and the ethereal solution was washed with water, dried over sodium sulfate and concentrated. The *ester* (VIb) (890 mg) showed m.p. 198–200°. The analytical sample was obtained by repeated crystallization from acetone–ether and showed brilliant plates with m.p. 206–207°; $[\alpha]_D$ −116°; λ_{max} 3, 5·8, 5·9 μ. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73·76; H, 9·15. Found: C, 73·16; H, 9·25.

The *acetate* (VIc) showed m.p. 159–160° (prisms from acetone–methanol); $[\alpha]_D$ −110°; λ_{max} 5·8, shoulder at 5·9. *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 72·08; H, 8·71. Found: C, 71·79; H, 8·67.

16α-*Carbomethoxyprogesterone* (VIIb)

The Oppenauer oxidation of the ester (Xb) (5 g) was carried out as described before. Crystallization of the *diketone* (VIIb) from acetone–methanol yielded 3 g, m.p. 151–153°. Recrystallization from acetone–methanol raised the m.p. to 157–158°; $[\alpha]_D$ +31°; λ_{max} 240 mμ; log ε 4·23; λ_{max} 5·8, 5·9, 6·05 μ. *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66. Found: C, 74·59; H, 8·49.

16α-*Carboxyprogesterone* (VIIa)

(i) *By saponification of* 16α-*carbomethoxyprogesterone* (VIIb). The diketone (VIIb) (1 g) was dissolved in methanol (30 ml) and a solution of potassium hydroxide (1 g) in water (4 ml) was added. The mixture was heated under reflux for 1 hr, diluted with water and acidified with hydrochloric acid. The precipitate was collected, washed thoroughly with water and, on crystallization from acetone–ether yielded 560 mg of (VIIa), m.p. 240–244°. The analytical sample obtained by several recrystallizations from acetone-ether showed m.p. 250–254°; $[\alpha]_D$ +17°; λ_{max} 240 mμ; log ε 4·22; λ_{max} 5·9, 6·05 μ. *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73·71; H, 8·44. Found: C, 73·43; H, 8·53.

(ii) *By alkaline hydrolysis of* 16α-*cyanoprogesterone* (III). To a solution of the diketone (III) (500 mg) in 40 ml of methanol a solution of potassium hydroxide (1 g) in 4 ml of water was added. Then the experiment was carried out as described above.

The 16α-carboxyprogesterone (170 mg) showed m.p. 238–242°; λ_{max} 240–242 mμ; log ε 4·22; $[\alpha]_D$ +16° (the mixture with the above specimen gave no depression in the m.p. and the infrared spectra were identical).

3,20-*Bisethylenedioxy*-16α-*carbomethoxy*-Δ^5-*pregnene* (VIII)

A solution containing 3 g of 16α-carbomethoxyprogesterone (VIIb) and toluene-*p*-sulfonic acid (400 mg) in benzene (600 ml) and ethylene glycol (40 ml) was heated under reflux for 20 hr, a Stark trap being used for the elimination of water. After completion of the reaction, a solution of sodium bicarbonate was added and the benzene layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was crystallized from methanol, to furnish the 1·7 g of *diketone* (VIII), m.p. 174–176°. Repeated crystallization raised the m.p. to 182–183° (needles from acetone-methanol); $[\alpha]_D$ −70°. *Anal.* Calcd. for $C_{27}H_{40}O_6$: C70·40; H, 8·75. Found: C, 70·92; H, 8·67.

16α-*Hydroxymethylprogesterone* (IXa, IXb).

A solution of 2 g of the diketal (VIII) in 25 ml of anhydrous tetrahydrofuran was added slowly to a slurry of 500 mg of lithium aluminum hydride in 80 ml of ether; the mixture was heated under reflux for 30 min, water was added to destroy the excess of lithium aluminum hydride, and the mixture was acidified with hydrochloric acid. The organic layer was washed with water, dried and evaporated, and the oily residue was dissolved in 20 ml of methanol with four drops of concentrated hydrochloric acid. The solution was heated under reflux for 15 min, and then diluted with water and extracted with ether; the extract was washed with water, dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 380 mg having m.p. 159–161°. Repeated crystallizations raised the m.p. to 166–168°; $[\alpha]_D$ +77°; λ_{max} 240–242 mμ; log ε 4·23; λ_{max} 3·59 (weak), 6·05 μ. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76·70; H, 9·36. Found: C, 76·42; H, 9·49.

Δ^5-3β-*Acetoxy*-20β-*hydroxy*-16α-*carbomethoxypregnene* (Xa).

To a solution of 2·6 g of Δ^5-3β-acetoxy-16α-carbomethoxypregnen-20-one (VIc) in 80 ml of tetrahydrofuran, 1 g of sodium borohydride and 0·3 ml of water were added. The mixture was heated under reflux for 1 hr, diluted with water and extracted

immediately with ether. The organic layer was washed with water, dried and evaporated. Crystallization of the residue from acetone–hexane yielded (Xa) in brilliant plates (1·05 g), m.p. 147–149°, which on recrystallization melted at 157–158°; [α] —78°; λ_{max} 3, 5·8 μ. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71·74; H, 9·15. Found: C, 71·81; H, 9·07.

Δ^5-3β,20β-*Dihydroxy*-16α-*carboxypregnene* (Xb)

The monoacetate (Xa) (550 mg) was dissolved in 50 ml of methanol and a solution of 800 mg of potassium hydroxide in 5 ml of water was added. The mixture was heated under reflux for 1 hr diluted with water and acidified with hydrochloric acid. The precipitate was collected and washed with water and, on crystallization from methanol, gave needles (275 mg) of the *acid* (Xb), m.p. 273–275°. The analytical sample showed m.p. 281–283°; [α] —84·5° (dioxan); λ_{max} 3, 5·95 μ (Nujol). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72·89; H, 9·45. Found: C, 72·74; H, 9·45.

Δ^5-3β-20β-*Diacetoxy*-16α-*carboxypregnene* (Xc).

The free diol (200 mg) was dissolved in 1·5 ml of acetic anhydride and 1·5 ml of pyridine, and the mixture was left at room temperature overnight. It was then poured into water, and the precipitate was extracted with chloroform and washed with hydrochloric acid and water. After concentration and addition of ether, the *diacetate* (Xc) crystallized as needles (210 mg), m.p. 210–212°, which on recrystallization from acetone–ether melted at 213–215°; $[\alpha]_D$ —53·5°; λ_{max} 5·8, shoulder at 5·9 μ. *Anal.* Calcd. for $C_{28}H_{38}O_6$: C, 69·93; H, 8·58. Found: C, 70·15; H, 9·19.

Acknowledgements—I am indebted to Dr. George Rosenkranz of Syntex S.A. for a generous gift of the steroids that were used in this work.

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ESTRANE DERIVATIVES—I*

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(*Received* 4 *October* 1957)

Abstract—Three of the four possible ring A/B isomeric estrane-17-ol-3-ones and their corresponding acetates, benzoates and diones were prepared for the purpose of biochemical studies. The positions of the hydrogens on C5 and C10 of these compounds have been assigned.

One of the estrane-3,17-diones prepared was, according to the double melting points, identical with one of the diones described by Marker and co-workers, obtained from non-pregnant urine source and and synthetic means.

SCHOELLER and associates[1] first accomplished the catalytic hydrogenation of estrone to a mixture of "octahydrofollicular hormones". They found this mixture of ring "A" saturated compounds, the estranes, to be active as androgens at 8–10 mg per capon unit. Such "A" ring hydrogenations were performed later by other investigators.[2–5]

Marker *et al.*[6] isolated two isomeric estranediols from human female non-pregnancy urine. One of the two isomers was identical with a compound prepared by hydrogenation of estrone in alcoholic solution over platinum.[5] On carrying out the hydrogenation in an acidic medium, Dirscherl obtained a third isomer.[4]

It seemed desirable to pursue the study of the estranediols and their derivatives further in regard to the influence of the angular methyl group C19 on their physiological properties, both in androgenic and in anabolic activities. The anabolic or myotrophic effects are of particular importance in view of recent biochemical developments.[7–9] From analogy with the metabolism of adrenal cortical hormones, androgenic hormones and progestrone, there are good reasons to believe that some metabolic products of 19-nortestosterone may be estranediols and derivatives. In the studies of the metabolism of estradiol-16-C^{14} in human female subjects, Beer and Gallagher[10,11] obtained up to 6 per cent "neutral fraction" from the total radioactivity of the urinary extract. It is possible that the "neutral fraction" contains ring "A" saturated compounds. Such a view would serve to explain the origin of the two estranediols isolated by Marker *et al.*[6]

Recently, it has been established that testosterone and cholesterol may be converted

* A part of the work described in this and subsequent papers was performed in 1940–1944 in Berlin, Germany, under the direction of Professor Walter Schoeller and in Basle, Switzerland, under the direction of Professor T. Reichstein.

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biologically to estrogens.[12–14] No evidence is, however, available that such conversion is obligatory. Indeed, it may play only a relatively minor role in the biosynthesis of estrogens. It is then possible that estranes or their unsaturated counterparts are the precursors of estrogens.

In this paper three of the possible four isomeric series of estrane compounds that differ in the spatial arrangement at C5 and at C10 or rings A/B are presented.

Hydrogenation of estradiol with platinum catalyst was sluggish and caused extensive hydrogenolysis on one or both hydroxy groups. Raney nickel catalyst was therefore selected. Rapid hydrogenation of estradiol-17-acetate (I) in *cyclo*hexane solution took place at about 120°. The hydrogenation products were immediately oxidized and chromatographically separated through alumina. Two estrane-17-ol-3-one acetates (II and III) in about equal amounts were obtained. When the hydrogenation was performed in methanol solution, transesterification sometimes took place as evidenced by the isolation of two diones (VI and VII) corresponding to the two acetates.

It was thought, because of the probable thermodynamic stability of the 10 β-compounds, both of the estraneolone acetates II and III would be 10 β in orientation, but the huge difference in optical rotation of the two compounds indicated otherwise.

Hydrogenation of nortestosterone, which has the 10 β-configuration[15] or its esters (X), with palladium catalyst produced two estrane-17-ol-3-ones or their esters (III, XI, IX, and XVI). The acetate of the predominant isomer acetate was identical with III obtainable from the hydrogenation of estradiol-17-acetate. Compound III was assigned the 5 α-, 10 β-isomeric form as in the case of the catalytic hydrogenation of testosterone[16] and by contrast with the products of the catalytic hydrogenation of cholestenone.[17] The minor hydrogenation product (XI) was not identical with II and was designated to be the 5 β-, 10 β-isomer. The assigned steric configuration was supported by the slightly positive optical rotatory power of XI as compared to III, and by the thermodynamic consideration that the *trans–anti–trans* (5 α, 10 β) isomer has the lowest energy and should be favored in its formation.[18,19] It was thus established that II was a 10 α-isomer. The position of the hydrogen on C5 of II is tentatively assigned the α-position, again on the basis of thermodynamic.

The three estrane-17-ol-3-one acetates II, III and XI were hydrolyzed to their parent compounds, estraneolones (IV, V and XII); they were in turn benzoylated and oxidized to their benzoates (VIII, IX and XIV) and estranediones (VI, VII and XIII).

It may be noted that of the three estranedions prepared only one, VII, could be identified with one of the two diketones described by Marker and associates[5,6]

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* A communication to the Editor has appeared since the preparation of this manuscript. A compound m.p. 130–132° (uncorrected), $[\alpha]_D + 60°$, to which was assigned the structure V (5 α) and is apparently identical with our compound XII (5 β), m.p. 133·5–4°, $[\alpha]_D^{23.5} + 52·8°$ (acetone), $[\alpha]_D^{23.5} + 50·5°$ (dioxane).

OAc
HO
I
Ni, H2, 120°
Cr2O3
m.p. 110°
(α)D −55·4° (acetone – a)
−57·0° (dioxane – d)
II
OAc
H
O
m.p. 135°/146°
(α)D −54·1° (a)
−59·8° (d)
IV
OH
m.p. 164°
(α)D +22·2° (a)
+17·9° (d)
VI
OBz
m.p. 202·5°
(α)D −21·8° (d)
VIII
m.p. 151°
(α)D +72° (d)
IX
m.p. 177°
(α)D +79·6 (d)
XIV
m.p. 114°/132·5°
(α)D +28·2° (a)
+20·8 (d)
III
m.p. 111°
(α)D +33·1° (a)
+29·3° (d)
V
m.p. ~150°/184°
(α)D +109·1 (a)
+104·7 (d)
VII
Pd, H2
X
m.p. 102°
(α)D +39·0° (a)
+35·6° (d)
XI
m.p. 133·5
(α)D +52·8° (a)
+50·5° (d)
XII
m.p. 70°
(α)D +127·3° (a)
+121·5° (d)
XIII

from non-pregnant urine source, as judged by its double melting points (lit. 144–6°/179–80°; found: ~150°/184–5°).

It should be emphasized here that our knowledge concerning the hormonal activities of steriods is limited to the 10 β-compounds. The synthesis of a 10 α-steroid may offer an opportunity for the investigation of spatial configuration and biological properties of this family of compounds.

EXPERIMENTAL*

Hydrogenation of estradiol-17-acetate (I).† Estradiol-17-acetate (1·62 g) in 50 ml *cyclo*hexane was hydrogenated for 4½ hr under 120 atmospheric pressure at 120° with 1 g of freshly prepared Raney nickel that had been washed carefully with methanol and *cyclo*hexane. After the solvent was removed, the glassy residue was oxidized with 250 mg chromic oxide in 37 ml glacial acetic acid pre-treated with chromic oxide. After standing at room temperature for 3 hr, all of the chromic acid was consumed. More chromic acid solution was added until there was an excess of chromic acid after 5 hr standing at room temperature. In all a total of 562 mg of chromic oxide was used. Three milliliters of methanol was added and the solution concentrated to dryness in vacuum at 30°. The residue was taken up in ether and washed with dilute sulfuric acid, sodium carbonate and water until neutral. After the ether solution was dried over anhydrous sodium sulfate and concentrated to dryness, 1·62 g glassy materal remained in the flask.

From an ether and pentane mixture, some crystals, m.p. 108–12°, could be obtained. However, the yield of the pure crystals was too small to be practical. The mixture was next subjected to chromatographic separation through 50 g aluminum oxide and developed with 150 ml portions of solvent or solvent mixture. From pentane–benzene (9 : 1) eluates, 508 mg of the first compound, estrane-17-ol-3-one acetate (II) was obtained. Rectangular or hexagonal crystals were obtained from ether and pentane mixture, m.p. 110–11°.

$[\alpha]_D^{23}$ −55·4°, M_D −176·3° (acetone); $[\alpha]_D^{23}$ −57·0°, M_D −181·5° (dioxane).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75·43; H, 9·50. Found: C, 75·58; H, 9·66.

From the benzene eluate a second estrane-17-ol-3-one-acetate (III) appeared. After two recrystallizations from ether pentane mixture, 137 mg of fine needles were obtained, m.p. 132–4°. Occasionally, it gave a double melting point of 114–16°/132·5–134·5°.

$[\alpha]_D^{15}$ +28·2°, M_D +89·8° (acetone); $[\alpha]_D^{23·5}$ +20·8°, M_D +65·1° (dioxane).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75·43; H, 9·50. Found: C, 75·05; H, 9·35.

Similar runs using methanol instead of *cyclo*hexane gave occasionally two diketones: m.p. 164° (VI) which appeared after II in the chromatogram and m.p. 184° (VII) which appeared after III in the chromatogram. Both compounds will be described later.

Estrane-17-ol-3-one (IV). Estrane-17-ol-3-one acetate (40 mg) (II, m.p. 110–11°) was hydrolyzed by refluxing for 45 min in a solution of 35 mg potassium hydroxide in 1 ml methanol. After the addition of 100 mg potassium bicarbonate in 2 ml water,

* The melting points were taken on a Kofler block and were corrected to ± 1·5;. The author is indebted to Dr. E. Thommen, Basle, Switzerland, for the microanalysis, as well as to Mr. Terry Yamauchi and Mrs. Bojana Kabalin for their technical assistance.

† The author wishes to express his appreciation for the assistance rendered by Professor Herman Pines of this University in the high pressure hydrogenation of one batch of the material in his laboratory.

the methanol present was removed in vacuum. The residue was extracted with ether. The ether extract was washed to neutral with water, dried over anhydrous sodium sulfate and concentrated to dryness, yielding 36 mg crystalline mass. Recrystallization from ether–pentane mixture gave 29 mg granular crystals, m.p. 135–36°/146–7·5°. $[\alpha]_D^{23}$ −54·1°, M_D −150·0° (acetone); $[\alpha]_D^{23.5}$ −59·8°, M_D 165·3° −(dioxane).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78·20; H, 10·20. Found: C, 78·22; H, 10·05.

Estranedione (VI). Estrane-17-ol-3-one (19 mg) (IV m.p. 133–34°) was dissolved in 0·35 ml purified glacial acetic acid and treated with 7 mg chromic oxide in 0·35 ml acetic acid for 14 hr at room temperature. After the reaction mixture was concentrated to dryness in vacuum at 30°, the residue was taken up in ether and washed with sulfuric acid, sodium carbonate and water until neutral, dried over anhydrous sodium sulfate and concentrated to dryness. Residue of 16 mg was obtained which crystallized from ether : pentane mixture as leaflets, m.p. 162–64°. The admixture of this product and the compound previously isolated from the mixture of oxidized hydrogenation products gave no depression. Upon further recrystallization, the m.p. rose to 164–66°. $[\alpha]_D^{13}$ +22·2°, M_D +60·9° (acetone); $[\alpha]_D^{23}$ +17·9°, M_D +49·1° (dioxane).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78·79; H, 9·55. Found: C, 78·70; H, 9·62.

Estrane-17-ol-3-one (V). Compound III (480 mg) (m.p. 129°) was hydrolyzed in similar manner as in VI, yielded 465 mg material, which upon two recrystallizations from acetone–hexane gave 420 mg silky crystals that melted at 111–12°. $[\alpha]_D^{23}$ + 33·1° M_D +91·4°; $[\alpha]_D^{23.5}$ +29·3°, M_D +81·0°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78·20; H, 10·20. Found: C, 78·10; H, 10·21.

Estrane-3, 17-dione (VII). Estrane-17-ol-3-one (60 mg) (V, m.p. 111°) was oxidized as in VI and yielded, after recrystallizations from *n*-hexane, 40 mg rod-shaped crystals, m.p. 184–85·5° which underwent, first a change of crystal form and sometimes actually melted at about 150°. $[\alpha]_D^{17}$ +109·1°, M_D +299·36° (acetone); $[\alpha]_D^{23}$ +104·7° M_D +287·2° (dioxane).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78·79; H, 9·55. Found: C, 78·79; H, 9·70.

Estrane-17-ol-3-one benzoate (VIII). Estrane-17-ol-3-one (55 mg) (IV, m.p. 133°) was reacted with 0·1 ml benzoyl chloride and 0·5 ml pyridine at room temperature for 16 hr. One milliliter of water was added and the solution kept at room temperature for ½ hr. It was then taken up in ether and washed with 2 N hydrochloric acid, 2 N sodium carbonate and water until neutral. The semi-oily material was chromatographed on 1·5 g alumina. All the *n*-hexane eluates were combined and recrystallized from acetone. Oblong or rectangular crystals thus obtained (37 mg) melted at 201–3°. For analysis the crystals were repeatedly recrystallized from methylene chloride–methanol and from acetone–hexane, irregular prisms, m.p. 204·5–6°, sweating began at 201°. $[\alpha]_D^{25}$ −21·8°, M_D −82·95° (dioxane).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78·91; H, 8·48. Found: C, 79·13; H, 8·67.

Estrane-17-ol-3-one benzoate (IX). Estrane-17-ol-3-one (65 mg) (V, m.p. 109–11°) was reacted with benzoyl chloride and pyridine in the same manner as in VIII. The gummy material obtained was subjected to chromatogram. Rod-shaped crystals obtained from an alumina column eluted with *n*-hexane–benzene (8 : 2) were combined

* The author wishes to thank Dr. John Babcock of the Upjohn Company for a generous gift of this material.

and recrystallized twice from acetone–*n*-hexane mixture; 50 mg, m.p. 151–53·5°, $[\alpha]_D^{25}$ +71·95°, M_D +273·77° (dioxane).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78·91; H, 8·48. Found: C, 79·00; H, 8·71

Estrane-17-*ol*-3-*one acetates* (III *and* XI). A 1·0 g sample of nortestosterone* was hydrogenated in 10 ml ethanol with 50 mg of palladium catalyst on charcoal at room temperature and slightly above atmospheric pressure. The hydrogenation was completed in 1 hr. After the removal of the catalyst and solvent, the glassy material was acetylated with pyridine and acetic anhydride at room temperature for 18 hr. The resulting acetate mixture was worked up in the usual manner. The oily residue was allowed to crystallize from a *n*-hexane solution. Repeated recrystallization from the same solvent afforded 619 mg estraneolone acetate (III), m.p. 114–15°/ 132·5–4·5°. The admixture of this compound with III, previously described, gave no melting point depression.

The mother-liquor was chromatographed once through 15·0 g alumina. The benzene–*n*-hexane (1 : 9) eluate, weighing 210 mg, was rechromatographed through 7·0 g alumina. From the benzene–*n*-hexane (1 : 9) eluate, 58 mg oblong crystals of estraneolone acetate (XI) were obtained. It was recrystallized once from *n*-pentane, m.p. 102–3°. The oblong crystals changed to fine needles at about 90°. $[\alpha]_D^{23·5}$ +39·0°, M_D +121·7° (acetone); $[\alpha]_D^{24}$ +35·6°, M_D +111·3° (dioxane).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75·43; H, 9·50. Found: C, 75·15; H, 9·47.

Estrane-17-*ol*-3-*one benzoates* (IX *and* XIV). Hydrogenation of a 378 mg sample of nortestosterone benzoate, m.p. 178–9°, in glacial acetic acid with palladium catalyst, yielded 46 mg estraneolone benzoate (XIV). It crystallized in clusters of needles from acetone–*n*-hexane solution, m.p. 177–8·5°. $[\alpha]_D^{23·5}$ +79·6°, M_D +302·8° (dioxane).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78·91; H, 8·48. Found: C, 78·77; H, 8·64.

From the same hydrogenation mixture, 194 mg estraneolone benzoate (IX) was obtained.

Similar hydrogenation of nortestosterone acetate (X) instead of nortestosterone benzoate gave approximately the same quantity of 5 α (III)- and 5 β (XI)-isomers.

Estrane-17-*ol*-3-*one* (XII). Both estraneolone acetate XI and estraneolone benzoate XIV gave, upon hydrolysis with sodium hydroxide in methanol, the free compound. Upon recrystallization from acetone–*n*-hexane mixture, hexagonal crystals were obtained, m.p. 133·5–4°. $[\alpha]_D^{23·5}$ +52·8°, M_D +146·0° (acetone); $[\alpha]_D^{23·5}$ +50·5°, M_D +139·5° (dioxane).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78·20; H, 10·20. Found: C, 78·22; H, 10·05.

Estrane-3, 17-*dione* (XIII). Sample of estraneolone (XII) (48 mg) was oxidized with chromic acid in acetic acid as in VI. This gave an oily material, which upon chromatographic purification yielded clusters of needles. Two recrystallizations from *n*-pentane gave 22 mg pure crystals, m.p. 70–70·5°. $[\alpha]_D^{23·5}$ +127·3°, M_D +349·2° (acetone); $[\alpha]_D^{23·5}$ +121·5°, M_D +333·4° (dioxane).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78·79; H, 9·55. Found: C, 78·83; H, 9·49.

Tetrahedron, 1958, Vol. 3, pp. 49–61. Pergamon Press Ltd., London

STUDIES ON PYRIDOXINE AND PYRIDOXAL ANALOGS—I*

THE SYNTHESIS OF SUBSTITUTED PYRIDINEALDEHYDES

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(*Received* 9 *December* 1957)

Abstract—The preparation, purification and properties of 3-hydroxypyridine-2-aldehyde, 3-methoxypyridine-2-aldehyde, 3-hydroxypyridine-4-aldehyde, 3-methoxypyridine-4-aldehyde and their derivatives and some new intermediates are reported. The preparation of the thio-semicarbazones of the aldehydes, as potential tuberculostatic agents, and of 3-hydroxy-4-hydroxymethylpyridine and 3-methoxy-4-hydroxymethylpyridine as pyridoxine analogs, are described.

DURING the last decade, the synthesis of a number of compounds as analogs and homologs of members of the vitamin-B_6 group has been reported.[1] All investigations on the course of vitamin-B_6 catalyzed biochemical reactions and their non-enzymatic counterparts with pyridoxine derivatives *in vitro* have led to the conclusion that the catalytically active site is a metal chelate of a Schiff base formed between an amino acid and pyridoxal(I), which in the form of a metal chelate is in equilibrium with the tautomeric Schiff base derived from pyridoxamine and a keto acid, as well as with other possible products. On this basis it seemed desirable to study the chelating properties and reactivities of a number of analogs of pyridoxal, in which only the essential hydroxyl and aldehyde groups are present. In this paper are described the synthesis of two such compounds, 3-hydroxypyridine-4-aldehyde(II) and 3-hydroxypyridine-2-aldehyde(III). In order to evaluate the influence of the 3-hydroxy groups on the stability and behavior of Schiff bases, those aldehydes with the hydroxyl group blocked by methylation(IV and V) were also prepared.

RESULTS AND DISCUSSION

The synthetic methods available for the preparation of compounds (II), (III), (IV) and (V) were limited by the fact that all *C*-substitution aldehyde synthetic procedures developed for aromatic compounds have failed to work for pyridine derivatives. Pyridine-2-aldehyde and -4-aldehyde have been obtained in only low yields by ozonolysis of benzylidenepicolines,[2,3,4,5,6] by oxidation of picolines with selenium dioxide[7] or by the McFadyen–Stevens method.[8,9,10] The Rosenmund reduction of

* This investigation was supported by a research grant A-1307 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

[1] D. E. Metzler, M. Ikawa and E. E. Snell, *J. Amer. Chem. Soc.* **76**, 648 (1954).
[2] J. P. Wibaut, E. C. Kooyman and H. Boer, *Rec. Trav. Chim. Pays-Bas* **64**, 30 (1945).
[3] L. C. Craig and M. Hixon, *J. Amer. Chem. Soc.* **53**, 4369 (1931).
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[8] P. Dayson and D. L. Hammick, *J. Amer. Chem. Soc.* **61**, 781 (1939).
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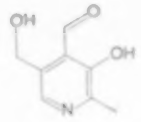
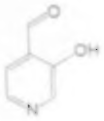
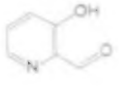
unsubstituted acid chlorides was unsuccessful,[9,11,12,13] although it proved satisfactory for the preparation of chlorinated aldehydes. The vapor-phase oxidation of the picolines described by Matthes *et al.*[14] is applicable only to volatile materials. Although pyridoxal and its homologs have been prepared from pyridoxine by mild oxidation



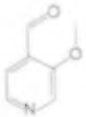
I



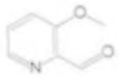
II



III



IV



V

with manganese dioxide[15–20] or (in low yield) with potassium permanganate,[21] such methods have not been employed successfully for the simple pyridinealdehydes. The procedures employed in this investigation are an improved method of oxidation with manganese dioxide and a modification of the reaction described by Wibaut and co-workers[22,23] between orthoformic esters and pyridylmagnesium compounds, and a modification of lead tetra-acetate oxidation of pyridinemethanols described by Micovic and Mihailovic.[24]

Pyridine-2-aldehydes

Although none of the four aldehydes reported in this paper have been described previously, two derivatives of 3-hydroxypyridine-2-aldehyde(III) have been reported. Kuhn and Hensel[25] oxidized 3-hydroxy-2-hydroxymethylpyridine and isolated an

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[14] W. Matthes, W. Sauermilch and Th. Klein, *Chem. Ber.* **84,** 452 (1951).
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[19] D. Heyl, E. Luz, S. A. Harris and K. Folkers, *J. Amer. Chem. Soc.* **75,** 4079 (1953).
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[21] S. A. Harris, D. Heyl and K. Folkers, *J. Amer. Chem. Soc.* **66,** 2088 (1944).
[22] J. P. Wibaut and H. G. P. van der Voort, *Rec. Trav. Chim. Pays-Bas* **71,** 798 (1952).
[23] J. P. Wibaut and R. Huls, *Rec. Trav. Chim. Pays-Bas* **71,** 1021 (1952).
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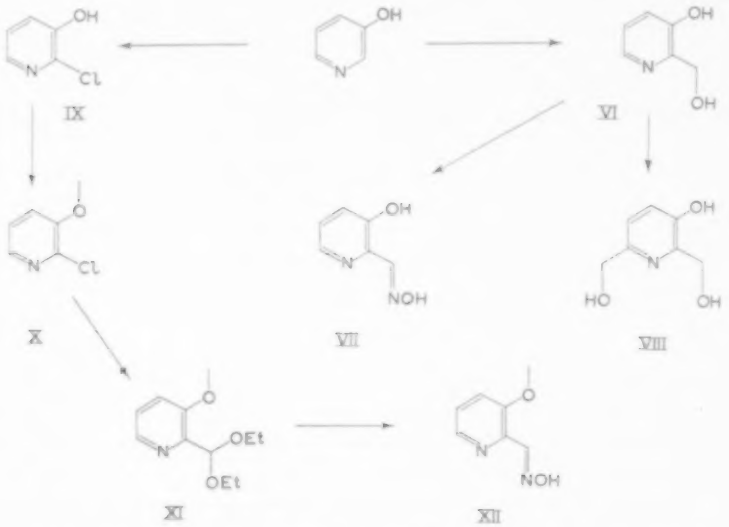
[25] R. Kuhn and H. R. Hensel, *Chem. Ber.* **86,** 1333 (1953).

oxime showing an intense lilac fluorescence in aqueous solution. In a similar manner, Metzler *et al.*[1] obtained an aldehyde preparation in the form of a sirup, estimated at 68 per cent pure,* and a solid 2,4-dinitrophenylhydazone. On the assumption that these investigators could not isolate the free aldehyde because of its possible sensitivity to further oxidation and self-condensation in aqueous solution, the oxidation was attempted with lead tetra-acetate in a mixture of benzene and acetic acid. Only low yields of the oxime were obtained, while the main product seemed to involve further oxidation. In order to stabilize the aldehyde by acetal formation, the oxidation was carried out with amorphous manganese dioxide in ethanol in the presence of triethyl orthoformate. In this way the free aldehyde, not the acetal, was isolated as lemon-yellow prisms with a pungent odor. The oxime(VII), prepared from the pure aldehyde, was obtained as colorless needles having only a slight blue fluorescence in aqueous solution and melting at 175–176°, 5° higher than the previously reported melting point. The 2,4-dinitrophenylhydazone had a melting point of 263·5–264·5°, more than 40° higher than that previously reported.

These deviations, which indicate that the previous compounds were not completely pure, probably result from the fact that the starting material (VI) used in the oxidation



had been obtained by the method of Urbanski,[26] which produces the 2,6-dimethanol (VIII) as well as the desired monosubstitution product. A series of experiments were therefore carried out with varying ratios of 3-pyridol to formaldehyde, but it was found that the disubstitution product was always formed, even when a large excess of pyridol was used. In all runs, the ruby coloration of the reaction mixture, which changes to green on acidification, noted by Urbanski[26] as an indication of the formation of open-chain products, was not observed. The color remained a light amber

* Recently S. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.* **79**, 481 (1957) attempted the preparation of III by a different method and of V by methylation of crude III with methy *p*-toluenesulfonate. Neither one of the aldehydes was obtained in crystalline form. The oxime of V, however, previously unknown, was isolated: m.p. 198–199°; this investigation, m.p. 196–197°.

[26] T. Urbanski, *J. Chem. Soc.* 1104 (1946).

throughout the reaction, in accordance with the observations of Stempel and Buzzi.[27] The problem of separating 3-pyridol(VI) and (VIII) was finally solved by fractional precipitation with gaseous hydrogen chloride of 3-pyridol and (VI) from acetone or ethanol, followed by treatment of the solid mixture with excess of hydrochloric acid and fresh solvent, whereby only 3-pyridol goes into solution.

It is not possible to use direct methylation of (III) to obtain the methoxyaldehyde (V), since methylating agents would also react with the carbonyl group or with the tertiary nitrogen atom. On the other hand, the new compound 2-chloro-3-methoxypyridine(X), prepared in 60 per cent yield from (IX) with diazomethane, offered the possibility of synthesizing (XI) by means of a Grignard reaction. Wibaut and coworkers[22,23] have modified the Grignard synthesis so that satisfactory yields are obtained for bromopyridines in spite of the insolubility of pyridylmagnesium bromide by carrying out the reaction at higher temperature in the presence of a reactive alkyl halide. Although the applicability of this method to *ortho*-substituted chloropyridines was somewhat doubtful because of the low reactivity of the chloride (compared to bromides and iodides) as well as the steric influence of the methoxy group, the reaction with ethyl orthoformate was found to proceed satisfactorily with the formation of the diethylacetal(XI), which was obtained in 30 per cent yield after two distillations.

The starting material (IX) was prepared by a modification of the method of Schickh *et al.*,[28] which consisted in chlorinating with a mixture of boiling hydrochloric acid and hydrogen peroxide. In this investigation it was found that the use of ultraviolet light during the chlorination increased the 50 per cent yield obtained by Schickh *et al.* to over 75 per cent. The free methoxyaldehyde(V) was finally produced in 50–60 per cent yield by hydrolysis of the acetal with hydrogen chloride in an atmosphere of nitrogen. A similar attempt to prepare the hydroxyaldehyde(III), through the reaction of the magnesium alkoxide of (IX) with more magnesium and ethyl orthoformate in the presence of an additional Grignard reagent, failed because of lack of solubility of the magnesium derivative.

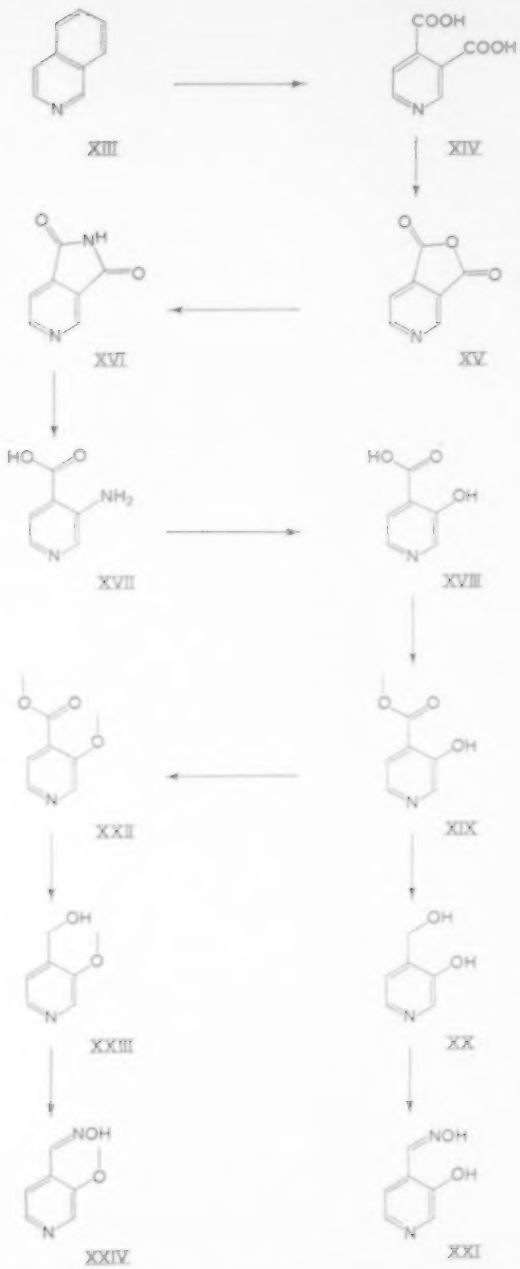
Pyridine-4-aldehydes

Of the few synthetic methods previously employed for the preparation of 3,4-disubstituted pyridines, the route outlined in the following scheme has turned out to be the least complicated. The starting material was 3-hydroxy*iso*nicotinate(XIX), which could be prepared from cinchomeronic acid(XIV) by methods reported in the literature, but which was prepared by somewhat modified procedures described under "Experimental".

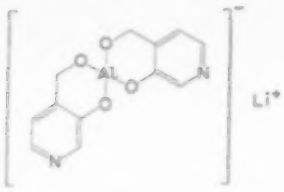
The compounds of the methoxy series were obtained by methylating (XIX) with diazomethane. This reaction proceeded much more slowly than that of the 2-chloro-3-hydroxypyridine described above, and an excess of diazomethane was needed to bring the reaction to completion. The slowness of the reaction is probably due to steric hindrance by the adjacent carboxymethyl group.

The reduction of (XXII) and (XIX) to the oxidizable pyridinemethanols was attempted with lithium aluminum hydride. While the reduction of (XXII) proceeded smoothly to give a good yield of 3-methoxy-4-hydroxymethylpyridine, the reduction of (XIX) required an excess of lithium aluminum hydride to allow the formation of the

[27] A. Stempel and E. C. Buzzi, *J. Amer. Chem. Soc.* **71**, 2969 (1949).
[28] O. V. Schickh, A. Binz and A. Schulz, *Ber. Dtsch. Chem. Ges.* **69B**, 2593 (1936).



aluminate of both hydroxyl groups. The primary reaction product of the reduction is believed to have structure (XXV). This salt was readily broken down with hydrochloric acid to give a 66 per cent over-all yield of (XX). While the methoxypyridinemethanol (XXIII) is soluble in organic solvents and was found in the ethereal layer of the reduction medium after hydrolysis, the hydroxypyridinemethanol(XX) was



XXV

found in the aqueous layer, and like its isomer (VI) is quite insoluble in ether and solvents of low polarity.

Oxidation of the pyridinemethanols was carried out as described above for 2-hydroxymethyl-3-pyridol with specially prepared manganese dioxide in ethanol. Commercial manganese dioxide was found to give only very low yields, because the crystals were not attacked by the acid. The manganese dioxide prepared by thermal decomposition of manganous carbonate was almost completely dissolved under the same reaction conditions. It is remarkable that the hydroxypyridinemethanols are more difficult to oxidize (requiring heating for 1 hr under reflux) and give much more colored side-products than the methoxypyridinemethanol(XXIII) which requires only 15 min for oxidation to the aldehyde.

The oximes (XXIV) and (XXI) as well as the corresponding thiosemicarbazones and 2,4-dinitrophenylhydrazones were isolated. The properties of the four aldehydes and their derivatives prepared in this investigation are compared in Table 1.

This work is being continued in the direction of preparing Schiff bases and metal chelates of all four pyridoxal analogs.

EXPERIMENTAL*

3-Hydroxy-2-hydroxymethylpyridine hydrochloride (VI)

To a solution of 3-pyridol (95 g, 1 mole) and sodium hydroxide (40 g) in water (400 ml), 38% formaldehyde solution (80 ml, 1 mole) was added. The clear mixture was warmed for 3 hr at 90°, then cooled to room temperature and acetic acid (60 g, 1 mole) was added. The water was removed under reduced pressure, the remaining viscous oil (or pale yellow solid) was stirred with acetone (1 l.) and the precipitated sodium acetate was filtered off. The solid was extracted with warm acetone (two 500 ml portions) and the combined extracts were further diluted with acetone (1 l.). The additional precipitate was then removed by filtration and the solution was concentrated under reduced pressure (to 1 l.). Hydrogen chloride gas was introduced at 0°, whereupon a colorless crystalline precipitate immediately formed. As soon as formation of the precipitate ceased, it was filtered off, washed with acetone (100 ml) and stirred with a saturated solution of hydrogen chloride in ethanol at 0° to dissolve unreacted pyridol. Filtration and washing with ethanol resulted in the isolation of a 45–50 per cent yield (75–80 g) of a nearly colorless solid. The product was purified by dissolving it in a minimum amount of warm water, treating with Norite, and adding a large volume of acetone at room temperature. The colorless crystals thus obtained darken above 180° and turned black at about 200°. *Anal.* Calcd. for

* All melting and boiling points are uncorrected.

TABLE 1. PHYSICAL PROPERTIES OF THE ALDEHYDES AND THEIR DERIVATIVES

Derivative	Property	(II)	(III)	(IV)	(V)
Free aldehyde	m.p.	126–128°	78–79°		55–56°
	color + form	yellow clusters	yellow clusters	colorless crystals	colorless crystals
	b.p.	—	64° (5 mm)	—	106–108° (3 mm)
Oxime	m.p.	205–206°	175–176°	160–161°	196–197°
	color + form	long colorless needles	long colorless needles	small colorless needles	short colorless rods
Thiosemicarbazone hydrochloride	m.p.	245–247° (dec.)	225–235° (dec.)	235–245° (dec.)	220–230° (dec.)
	color + form	dark-yellow leaflets	orange needles	lemon-yellow short needles	orange-yellow needles
2,4-Dinitrophenyl-hydrazone hydro-chloride	m.p.	323–325° (dec.)	253–254·5° (dec.)	256–258° (dec.)	269–270° (dec.)
	color + form	yellow powder	orange powder	lemon-yellow needles	orange-yellow needles

$C_6H_7O_2N \cdot HCl$: C, 44·6; H, 5·0; Cl, 21·9; N, 8·7. Found: C, 44·7; H, 4·8; Cl, 22·0; N, 8·7.

3-Hydroxypyridine-2-aldehyde (III)

3-Hydroxy-2-hydroxymethylpyridine hydrochloride (16·2 g, 0·1 mole) and amorphous manganese dioxide (8·7 g, 0·1 mole), prepared by heating manganese carbonate for 12 hr at 300°, were suspended in ethanol (200 ml), heated with stirring to reflux temperature and 96% sulfuric acid (10·2 g, 0·1 mole) in ethanol (50 ml) was added over a period of 30 min. After additional heating under reflux for 1 hr, the black solid turned brown and the pH rose to 6. The reaction mixture was cooled to 40° and filtered. The dark yellow solution was diluted with water (200 ml) and manganous carbonate was precipitated by adding excess of sodium bicarbonate. The filtrate was extracted with ether (one 400 ml and two 150 ml portions) and the combined ether extracts were extracted with 3·7% hydrochloric acid (four 25 ml portions, containing 0·1 mole of HCl). The acidic extracts were freed from ethanol *in vacuo*, adjusted to pH 7 with sodium bicarbonate, and extracted with ether (three 100 ml portions). To the yellow extracts, dried for 12 hr over anhydrous sodium sulfate and concentrated to a small volume (40 ml), hexane (50 ml) was added and the solution,[5] treated with Norite at 50° and filtered, gave on slow cooling star-shaped clusters of yellow crystals. The yield was 40 per cent (5 g) after recrystallization from hexane and washing with ligroin (boiling range 30–60°). *Anal.* Calcd. for $C_6H_5O_2N$: C, 58·5; H, 4·1; N, 11·4. Found: C, 58·1; H, 4·1; N, 11·3.

Preparation of derivatives. A solution of the aldehyde hydrochloride, prepared as described above from the pyridinemethanol by oxidation, extraction with ether and re-extraction with diluted hydrochloric acid, was generally used for the preparation of derivatives, which were subsequently obtained in analytical pure form after one recrystallization.

3-Hydroxypyridine-2-aldehyde-2,4-dinitrophenylhydrazone hydrochloride. A solution of the aldehyde hydrochloride, warmed with excess of 2,4-dinitrophenylhydrazine solution in 5% hydrochloric acid, rapidly deposited a precipitate of the product. Recrystallization from a large volume of aqueous ethanol containing some hydrochloric acid resulted in the isolation of an orange powder melting at 253·5–254·5°.

3-Hydroxypyridine-2-aldehyde-thiosemicarbazone hydrochloride. A solution of the aldehyde hydrochloride (0·1 mole) was added to a slurry of thiosemicarbazide (9·1 g, 0·1 mole) in ethanol (150 ml) and acetic acid (15 ml). The intense yellow solution, after being heated under reflux for 20–30 min, deposited orange needles on cooling. Purification by recrystallization from 4% aqueous hydrochloric acid and washing the product with absolute ethanol gave orange needles that decomposed at 225–235° without melting. *Anal.* Calcd. for $C_7H_9ON_4ClS \cdot 2H_2O$: C, 31·3; H, 4·9; N, 20·8; Cl, 13·2. Found: C, 31·3; H, 4·19; N, 20·7; Cl, 13·4.

3-Hydroxypyridine-2-aldoxime. A solution of the aldehyde hydrochloride (0·1 mole), sodium acetate (15 g) and hydroxylamine hydrochloride (14 g, 0·2 mole) was warmed at 100° for 20 min. After the mixture had been set aside for 2 hr at 0° and the vessel had been scratched, the product crystallized from the reaction mixture. Recrystallization from boiling water with addition of Norite gave long colorless needles, m.p. 178–179°. *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52·2; H, 4·4; N, 20·3. Found: C, 52·0; H, 4·4; N, 19·9.

2-Chloro-3-hydroxypyridine (IX)

Into a solution of 3-pyridol (95 g, 1 mole) in 37% hydrochloric acid (585 ml, 6 moles), heated with stirring to reflux temperature, 30% hydrogen peroxide (285 ml, 2·5 moles) was dropped slowly under the ultraviolet radiation of a 140 watt lamp (Hanovia type 30,600, without filter) applied from outside the reaction vessel. After 5 min of additional heating under reflux, water was distilled off under reduced pressure until a thick slurry of orange crystals of 2-chloro-3-hydroxypyridine hydrochloride was obtained. Ammonia gas was then introduced into the suspension at 0° until the pH rose to 8, and the dark reaction mixture was extracted with ether (five 200 ml portions). The residue was filtered off and the liquid was extracted continuously with ether (500 ml) for 24 hr. The combined ether extracts, after being dried over anhydrous sodium sulfate, gave after evaporation of the ether a residue of slightly yellow crystals in 70 per cent yield (90 g), or a rapidly crystallizing oil. The product was recrystallized three times from boiling water, and the oil containing higher chlorinated products was discarded. A 25–30 per cent yield (32–40 g) of colorless needles (m.p. 164–165° in a sealed tube) was obtained. *Anal.* Calcd. for C_5H_4ONCl: N, 10·8; Cl, 27·4. Found: N, 10·8; Cl, 27·3.

2-Chloro-3-methoxypyridine (X)

To a solution of 2-chloro-3-hydroxypyridine (64·5 g, 0·5 mole) in ether (250 ml) and ethanol (100 ml), an ether solution of diazomethane (containing at least 1 mole of

CH_2N_2[29] was added dropwise to keep nitrogen evolution under control. After the reaction product had been set aside at 20° for 12 hr, the color was dark red. The solvents were removed by distillation and the remaining dark red oil, which crystallized on cooling, was extracted with boiling ether (three 200 ml portions). The combined ether solutions were washed twice with water (100 ml), dried for 12 hr over anhydrous sodium sulfate, the ether was evaporated, and the remaining pale-yellow crystals were purified by treatment with Norite and recrystallization from light petroleum boiling range 30–60°). A 50–60 per cent yield (36–43 g) of colorless flat long needles of narcotic odor were obtained, m.p. 48–49°. *Anal.* Calcd. for C_6H_6ONCl: C, 50·2; H, 4·2; N, 9·7. Found: C, 50·2; H, 4·2; N, 9·7.

3-*Methoxypyridine-2-aldehyde diethylacetal* (XI)

A solution of 2-chloro-3-methoxypyridine(X) (14·4 g, 0·1 mole) and ethyl bromide (30 g, 0·27 mole) in absolute ether (100 ml) was dropped into a vigorously stirred mixture of magnesium turnings (9·8 g, 0·4 mole), absolute ether (20 ml) and ethyl bromide (3 g, 0·03 mole), in which a Grignard reaction had been started at such a rate that the reaction proceeded at a moderate rate. After additional heating under reflux for 30 min, the main part of the ether (80 ml) was distilled off, and benzene (100 ml, dried over calcium hydride) was added to dissolve the ether-insoluble pyridylmagnesium salts. The reaction mixture was cooled to 30° and triethyl orthoformate (60 g, 0·4 mole) was added. The reaction was started by brief warming in a water bath, and maintained by dropwise addition of the orthoester. The product, which separated into two phases, was heated under reflux for 20 min with stirring, and then cooled to 30° and treated with a 30% aqueous solution of ammonium chloride (250 ml). As soon as the lower layer (dark viscous oil) had dissolved, the unreacted magnesium and some tar were removed by filtration, the benzene layer was removed, and the aqueous layer was extracted with ether (six 50 ml portions). The benzene and ether solutions were combined, dried with anhydrous sodium sulfate and extracted with 96% sulfuric acid (6 g, 0·05 mole) in water (six 25 ml portions). The extracts were washed with ether (two 100 ml portions), adjusted to pH 9 with 30% aqueous sodium hydroxide and extracted with ether (four 100 ml portions). The dried extracts (left for 12 hr in contact with anhydrous sodium sulfate) were fractionated *in vacuo*. A fraction boiling at 58° (3 mm) consisting of 3-methoxypyridine was separated from the one boiling above 100° (3 mm). Redistillation gave the pure acetal as a pale yellow oil, b.p. 120° (3 mm). The yield was 30 per cent (6·3 g) of the theoretical amount. *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62·5; H, 8·1; N, 6·6. Found: C, 62·4; H, 7·7; N, 6·8.

3-*Methoxypyridine-2-aldehyde* (V)

A solution of the diethylacetal(XI) (21·1 g, 0·1 mole) in 10% hydrochloric acid (200 ml) was heated under reflux in a nitrogen atmosphere for 1 hr. The dark-yellow solution was adjusted to pH 10 with 30% sodium hydroxide and extracted with chloroform (four 100 ml portions). The combined extracts were dried with anhydrous sodium sulfate and fractionated *in vacuo*, when a 50–60 per cent yield (7–8 g) of a pale yellow oil, b.p. 106–108° (3 mm), which crystallized on cooling, was obtained. Recrystallization from benzene gave colorless leafets, m.p. 55–56°. *Anal.* Calcd. for $C_7H_7O_2N$: C, 61·3; H, 5·2; N, 10·2. Found: C, 61·9; H, 5·8; N, 9·8.

[29] B. Eistert, *Neuere Methoden der Organischen Chemie*. Verlag Chemie (1948).

Preparation of derivatives of (V). A solution of the aldehyde hydrochloride obtained by hydrolysis of the diethylacetal gave analytically pure derivatives in procedures similar to those described above.

2,4-*Dinitrophenylhydrazone hydrochloride of* (V). By means of the general procedure described above for (III), an orange-yellow crystalline powder, m.p. 269–270°, was obtained.

Thiosemicarbazone hydrochloride of (V). By the procedure described above for (III), orange-yellow needles, m.p. 220–230° (dec.), was obtained in 80–90 per cent yield. *Anal.* Calcd. for $C_8H_{11}ON_4ClS$: C, 38·9; H, 4·5; N, 22·7. Found: C, 38·8; H, 4·5; N, 23·1.

Thiosemicarbazone of (V). The concentrated aqueous solution of the hydrochloride obtained by the general procedure described above for (III) was warmed with sodium acetate and adjusted to pH 6 with sodium bicarbonate. Addition of ethanol and cooling produced yellow crystals, which were recrystallized from aqueous 10% ethanol to give a 50 per cent yield, m.p. 204–205° (dec.). *Anal.* Calcd. for $C_8H_{10}ON_4S$: C, 45·7; H, 4·8; N, 26·7· Found: C, 45·6; H, 4·6; N, 27·0.

3-*Methoxypyridine*-2-*aldoxime*(XII). The *oxime* prepared as described above for (III) was obtained as a 55 per cent yield of short colorless needles, m.p. 196·5–197·5°. *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55·2; H, 5·3; N, 18·4. Found: C, 55·2; H, 5·3; N, 18·4·

Pyridine-3,4-*dicarboxylic acid* (XIV)[30] (*cinchomeronic acid*)

*iso*Quinoline (129·2 g, 1 mole) was oxidized with 96·5% sulfuric acid (1350 g, 10 moles and 33 per cent excess), with selenium (2·4 g, 0·03 mole) as catalyst. For this operation, sulfuric acid (750 g) was heated with powdered selenium (1·4 g) in a three-necked flask provided with a stirrer, thermometer, dropping funnel and an air condenser connected to a wide gas-outlet tube to dispose of the sulfur dioxide and water produced in the reaction. The selenium dissolved completely as soon as the temperature reached 280°. Powdered selenium (1 g) was dissolved in 96% sulfuric acid (50 g) by heating and stirring at 250° for a few minutes, and the resulting green solution was allowed to cool down to 30° and was then added to the cooled solution of the *iso*quinoline (129·2 g) in 96% sulfuric acid (550 g). The mixture thus obtained was dropped into the heated and stirred sulfuric acid at such a rate that the temperature was maintained between 270 and 280°. After completion of the addition, the reaction mixture was kept at 280° for 1 hr. It was then allowed to cool down and the viscous reaction product was poured over crushed ice (400 g). The solution thus obtained was boiled for 5 min with activated carbon (5 g), the carbon and selenium were removed, and the cooled filtrate was brought to pH 1·5 by addition of 29% aqueous ammonia. The precipitate cinchomeronic acid was washed with a large amount of water and dried at 110° to give a 60 per cent yield (100 g) of a white amorphous powder, m.p. 256°.

Pyridine-3,4-*dicarboxylic acid imide* (XVI) (*cinchomeronimide*)

The imide (XVI) was prepared in 70–85 per cent yield from the anhydride (XV),[31] or better without isolation of (XV),[32] and was recrystallized once from acetic acid.

[30] M. B. Mueller, *U.S. Pat.* 2,436,660 (1948); *Chem. Abstr.* **42**, 4203 h (1948).
[31] G. B. Bachman and R. S. Barker, *J. Org. Chem.* **14**, 97 (1949).
[32] K. C. Blanchard, E. H. Dearborn, L. C. Lasagna and E. L. Buhle, *Bull. Johns Hopkins Hosp.* **91**, 330 (1952).

3-Aminopyridine-4-carboxylic acid (XVII)

The amino acid (XVII) was obtained in 55 per cent yield from (XV) by the method of Blanchard *et al.*[32]

3-Hydroxypyridine-4-carboxylic acid (XVIII)

The amino group of (XVII) was converted to hydroxyl in 65 per cent yield.[32] The product was recrystallized from a large volume of boiling water with the addition of Norite.

3-Hydroxypyridine-4-carboxylic acid methyl ester (XIX)

3-Hydroxypyridine-4-carboxylic acid(XVIII) (139·1 g, 1 mole) was heated under reflux with a mixture of methanol (220 ml, 7 moles), 96·5% sulfuric acid (152 g, 1·5 mole) and 1,2-dichloroethane (480 ml) for 20 hr. The unreacted acid was precipitated from the cooled reaction mixture on dilution with water (600 ml) and was recovered by filtration (42 g). The filtrate was neutralized with sodium bicarbonate and extracted with chloroform (six 150 ml portions). The combined extracts were dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure. The crystalline residue that remained (83 g, 85 per cent yield based on the hydroxy acid) was purified by recrystallization from light petroleum (800 ml, boiling range 60–110°), when pale-yellow thick crystals of aromatic odor were obtained. (75 g, m.p. 79–80°, in agreement with the literature[33]).

3-Methoxypyridine-4-carboxylic acid methyl ester (XXII)

A solution of diazomethane in ether (containing at least 1 mole of CH_2N_2) was added all at once to a solution of 3-hydroxypyridine-4-carboxylic acid methyl ester (XIX) (153·1 g, 1 mole) in ether (3 l.). After addition of ethanol (125 ml), the reaction began slowly with gas development and deepening of color. After the mixture had been set aside for 12 hr at room temperature, the solvents were removed under reduced pressure, and the dark red oily product that crystallized on cooling was extracted with boiling hexane (2 l.). After treatment with Norite, the yellow solution deposited colorless crystals and some oil. After repeated crystallizations from hexane, a 70 per cent yield (117 g) of short colorless needles, m.p. 55–56°, was obtained. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57·5; H, 5·4; N, 8·4. Found: C, 57·3; H, 5·5; N, 8·1.

3-Hydroxy-4-hydroxymethylpyridine hydrochloride (XX)

A solution of 3-hydroxypyridine-4-carboxylic acid methyl ester (XIX) (15·3 g, 0·1 mole) in ether (250 ml, dried over lithium aluminum hydride) was dropped slowly with stirring into a suspension of lithium aluminum hydride (8·5 g, 0·23 mole) in ether (250 ml, dried over lithium aluminum hydride). After the initial violent reaction, in which a thick precipitate formed, had slowed down, the mixture was warmed to reflux temperature for 10 min and was then cooled to room temperature. Ethyl acetate (27 g) was added dropwise in order to destroy the excess of hydride, and water (20 ml) was subsequently added to decompose the lithium alkoxides. The reaction mixture was filtered, and the solid obtained was extracted with boiling ethanol (two 250 ml portions) and then with boiling water (two 250 ml portions). The aqueous extracts were combined and adjusted to pH 4 by the addition of acetic acid, the water

[32] H. H. Fox, *J. Org. Chem.* **17**, 547 (1952).

was distilled off *in vacuo*, and the oily slowly crystallizing residue was dissolved in a mixture of ethanol (50 ml) and acetone (500 ml). Acetone was added until precipitation of lithium acetate was complete, and the yellow solution was filtered and concentrated *in vacuo* (to 500 ml), and the hydrochloride was precipitated with hydrogen chloride gas at 0°. The fine crystalline product was filtered off, washed with acetone and purified by being dissolved in water (15 ml), Norite (1 g) added, and precipitated with acetone (1200 ml). A 66 per cent yield (10·7 g) of pale-yellow leaflets was obtained, m.p. 198–202°. *Anal.* Calcd. for $C_6H_8O_2ClN$: C, 44·6; H, 5·0; Cl, 21·9; N, 8·7. Found: C, 44·5; H, 4·8; Cl, 22·0; N, 8·6.

3-*Methoxy*-4-*hydroxymethylpyridine* (XXIII)

A solution of 3-methoxypyridine-4-carboxylic acid methyl ester(XXII) (16·7 g, 0·1 mole) in ether (250 ml, dried over lithium aluminum hydride) was added dropwise in the course of 1 hr to a suspension of lithium aluminum hydride (9·5 g, 0·25 mole) in ether (250 ml, dried), which had been stirred for 10 min in a nitrogen atmosphere. A white precipitate formed locally, but when the mixture was stirred it dissolved almost completely in the lithium aluminum hydride solution. While the mixture was being cooled with ice-water, ethyl acetate (35·2 g, 0·4 mole) was added to destroy the excess of hydride. The lithium compounds were decomposed by adding cold water (18 ml, 1 mole) and the ethereal solution was separated from the hydroxide precipitate by filtration. The solid was extracted twice with ether (100 ml) and the combined ether solutions, after being dried with anhydrous sodium sulfate for 5 hr, were evaporated under reduced pressure. The remaining yellow oil, which crystallized completely on cooling, was purified by extraction with hexane in a continuous extractor. Most of the product was obtained in the form of colorless crystals in the extraction flask, while the solvent deposited only a small amount of substance on cooling, and the dark-red tarry impurities remained in the extraction thimble. A 46–50 per cent yield (6·4–7·0 g) of pale yellow crystals, soluble in water, ethanol, ether and hot benzene, but insoluble in ligroin (boiling range 30–60°) and cold hexane, was obtained, m.p. 113–114° (after recrystallization from benzene–hexane). *Anal.* Calcd. for $C_7H_9O_2N$: C, 60·4; H, 6·5; N, 10·1. Found: C, 59·9, H, 6·5; N, 9·7.

The hydrochloride, m.p. 206–207°, was obtained as colorless crystals in 80 per cent yield by addition of ethanolic hydrogen chloride to a solution of (XXIII) in ethanol at 0°.

3-*Hydroxypyridine*-4-*aldehyde* (II)

A suspension of 3-hydroxy-4-hydroxymethylpyridine hydrochloride(XX) in ethanol was oxidized and treated as described above for the isomeric 2-aldehyde(III). A yield of 30–40 per cent of yellow clusters of short crystals, m.p. 126–128°, was obtained. *Anal.* Calcd. for $C_6H_5O_2N$: C, 58·5; H, 4·1; Found: C, 58·0; H, 4·4.

2,4-*Dinitrophenylhydrazone hydrochloride of* (II). The oxime was obtained as a yellow crystalline powder, m.p. 323–325° (dec.), by the general procedure described above.

Thiosemicarbazone hydrochloride of (II). Small dark yellow leaflets of the *thiosemicarbazone* were obtained in 30 per cent yield, m.p. 245–247° (dec.), by the general procedure described above for (III). *Anal.* Calcd. for $C_7H_9ON_4ClS$; C, 36·1; H, 3·9; N, 24·1; Cl, 15·2. Found: C, 35·9; H, 3·9; N, 24·1; Cl, 15·2.

3-*Hydroxypyridine-4-aldoxime* (XXI). The *oxime* was obtained in 30 per cent yield as long colorless needles, m.p. 205–206°, by the general procedure described above. *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52·5; H, 4·4; N, 20·3. Found: C, 51·8; H, 4·4; N, 19·5.

3-*Methoxypyridine-4-aldehyde* (IV)

A suspension of the hydrochloride of 3-methoxy-4-hydroxymethylpyridine(XXIII) in ethanol was oxidized and processed as described above for (III). A 60 per cent yield of colorless crystals was obtained. *Anal.* Calcd. for $C_7H_7O_2N$: C, 61·3; H, 5·2. Fount: C, 61·9; H, 5·6.

2,4-*Dinitrophenylhydrazone hydrochloride of* (IV). The 2,4-dinitrophenylhydrazone was obtained as described above for (III) in 60 per cent yield as lemon-yellow needles, which were recrystallized from hot water, m.p. 256–258° (dec.).

Thiosemicarbazone hydrochloride of (IV). The *thiosemicarbazone* prepared by the procedure described for (III) was obtained as lemon-yellow needles, almost insoluble in ethanol, m.p. 235–245° (dec.). *Anal.* Calcd. for $C_8H_{11}ON_4ClS$: C, 38·9; H, 4·5; N, 22·7; Cl, 14·4. Found: C, 39·1; H, 4·5; N, 22·7; Cl, 14·3.

3-*Methoxypyridine-4-aldoxime*(XXIV). The *aldoxime* was obtained in 75 per cent yield as colorless needles, m.p. 160–161°, by the procedure described above for the oxime of (III). *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55·3; H, 5·3; N, 18·4. Found: C, 55·1; H, 5·3; N, 18·6.

Tetrahedron, 1958, Vol. 3, pp. 62–67. Pergamon Press Ltd., London

ANTHRAQUINONE AND ANTHRONE SERIES—XXII*

3:4:9:10-DIBENZOPYRENE AND PENTAPHENE FROM INDANTHRENE SCARLET 4G AND MAYVAT BRILLIANT RED AF

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Abstract—Mayvat brilliant red AF has been identified as a halogenated derivative of 3:4:9:10-dibenzopyrene-5:8-quinone (II), the latter being obtained by dehalogenation of Mayvat brilliant red AF or Indanthrene scarlet 4G with Raney nickel, aqueous sodium hydroxide and hydrogen. Reduction of (II) with aluminium tri*cyclo*hexoxide gave 3:4:9:10-dibenzopyrene (I), a potent carcinogen, which was isolated by Bonnet and Neukomm from tobacco smoke. Oxidation of 3:4:9:10-dibenzopyrene-5:8-quinone with chromic acid in glacial acetic acid gave pentaphene-5:14:8:13-diquinone (V). Reduction of (V) with aluminium tri*cyclo*hexoxide yielded pentaphene (VI). Condensation of (V) with hydrazine gave 1:2-diaza-3:4:9:10-dibenzopyrene-5:8-quinone (VII), reduction of which with aluminium tri*cyclo*hexoxide gave 1:2-diaza-3:4:9:10-dibenzopyrene (VIII).

ACCORDING to a report, Buu-Hoï isolated 3:4:9:10-dibenzopyrene (I) from tobacco smoke and found that "when the substance was injected into 4000 mice, each of them developed cancer. In some cases the growth took only 42 days to show itself. Half a mg was the amount given." The presence of 3:4:9:10-dibenzopyrene (I) in con-

(I)

(II)

siderable quantity in the neutral fractions of tobacco tar was in fact demonstrated by Bonnet and Neukomm;[1] Lacassagne *et al.*[2] compared the carcinogenic activities of (I) and its 5-methyl and 5:8-dimethyl derivatives, and observed that, after a subcutaneous injection of 0·6 mg of one of the three compounds, (I) produced sarcoma on the 42nd day in eleven mice. The 5-methyl derivative produced sarcoma in three out of ten mice after 150 days, and the 5:8-dimethyl derivative was inactive or feebly active.

3:4:9:10-Dibenzopyrene (I) was prepared by Scholl and Neumann[3] by distilling the 5:8-quinone (II) with zinc dust; Clar[4] obtained a yield of about 85 per cent by his technique of distillation with a mixture of zinc dust, zinc chloride and sodium chloride, but Buu-Hoï and Lavit[5] have reported a yield of 53·3 per cent.

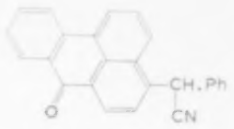
* Part XXI *J. Sci. Ind. Res.* B **16** 392 (1957).

[1] J. Bonnet and S. Neukomm, *Helv. Chim. Acta* **39**, 1724 (1956).
[2] A. Lacassagne, F. Zaideta, N. P. Buu-Hoï and H. Chalvet, *C. R. Acad. Sci., Paris* **244**, 273 (1957).
[3] R. Scholl and H. Neumann, *Ber. Dtsch. Chem. Ges.* **55**, 118 (1922).
[4] E. Clar, *Ber. Dtsch. Chem. Ges.* **72**, 1645 (1939).
[5] N. P. Buu-Hoï and D. Lavit, *Rec. Trav. Chim. Pays-Bas* **75**, 1194 (1956).

The quinone (II) can be prepared by the Scholl cyclisation of 1:4-dibenzoylnaphthalene or 4-benzoylbenzanthrone (III) with aluminium chloride.[3,6] An excellent method for the preparation of 4-benzoylbenzanthrone (III) is the condensation of benzanthrone with benzyl cyanide in presence of an alkali, followed by oxidative hydrolysis of the product (IV).[7]

Indanthrene scarlet 4G has been stated[6] to be the dibromo derivative of (II) and

(III)



(IV)

through the courtesy of Cassella Farbwerke, Mainkur, we obtained a sample of the dye, which contained both chlorine and bromine. It was dehalogenated by being shaken with sodium hydroxide solution, Raney nickel and hydrogen, and yielded the quinone (II). Anthraquinone undergoes reduction to 1:2:3:4-tetrahydroanthraquinone on being heated with Raney nickel and sodium hydroxide solution at water-bath temperature,[8] but the quinone (II) was unaffected under these conditions. Indanthrene scarlet 4G and Mayvat brilliant red AF were merely dehalogenated to the quinone (II) on being heated with Raney nickel and sodium hydroxide solution. Reduction of (II) with aluminium tri*cyclo*hexoxide in *cyclo*hexanol[9] readily gave the hydrocarbon (I), m.p. 281°, in 70 per cent yield. The general method for the reduction of quinones to hydrocarbons by treatment of the sulphuric ester of the leuco derivative with Raney nickel and sodium hydroxide[10] was also applicable, and will be described separately. A preliminary examination of Mayvat brilliant red AF, which dyes cotton a brilliant bluish red shade from a blood-red vat, showed that it was a halogenated quinone containing chlorine and bromine, but no nitrogen or sulphur. The dye, after removal of water-soluble matter, was found to be chromatographically homogeneous, when molten naphthalene was used as solvent and alumina as adsorbent. It crystallised from *o*-dichlorobenzene in red needles and sublimed without decomposition. Dehalogenation of the dye with sodium hydroxide, Raney nickel and hydrogen yielded the parent quinone (A), crystallising in red needles, m.p. 373°, identical with the quinone (II) obtained by dehalogenation of Indanthrene scarlet 4G.

The dehalogenated quinones from both Mayvat brilliant red AF and Indanthrene scarlet 4G gave identical derivatives by reductive acetylation and by reductive benzoylation.

Reduction of the quinone (A) with aluminium tri*cyclo*hexoxide[9] in *cyclo*hexanol gave 3:4:9:10-dibenzopyrene, identical with the hydrocarbon obtained from (II), as shown by the analysis, m.p. and mixed m.p. and absorption spectrum. On oxidation of the hydrocarbon with boiling aqueous chromic acid, the quinone (II) was obtained.

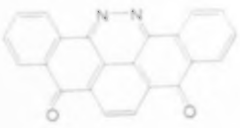
[6] K. Venkataraman, *The Chemistry of Synthetic Dyes*, Vol. II, p. 955. Academic Press, New York (1952).
[7] *D.R.P.* 501, 082; *D.R.P.* 568, 783; N. Campbell *et al.*, *J. Chem. Soc.* 1816 (1950); *Ibid* 3429 (1953).
[8] V. Ramanathan, B. D. Tilak and K. Venkataraman, *Proc. Indian Acad. Sci.* A **38**, 161 (1953).
[9] S. Coffey and V. Boyd, *J. Chem. Soc.* 2468 (1954).
[10] N. B. Desai, V. Ramanathan and K. Venkataraman, *J. Sci. Ind. Res.* B **14**, 330 (1955); *Ibid.* B **15**, 279 (1956).

The quinone (A) from Mayvat brilliant red AF was unaffected by oxidation with chromic acid in boiling aqueous sulphuric acid or treatment with alkaline potassium permanganate; but oxidation with chromic acid in boiling acetic acid converted (A) to a yellow crystalline quinone (B), m.p. 332°, which gave an orange vat, and was identified as pentaphene-5:14:8:13-diquinone (V).[3] Reduction of (B) with aluminium tri*cyclo*hexoxide[9] gave a 91 per cent yield of pentaphene (VI), identified by its m.p. and absorption spectrum. This route to pentaphene is much more convenient than the earlier methods, such as the Elbs pyrolysis of 2:4-dibenzoyl-*m*-xylene[11] or the synthesis starting from the Grignard reaction between phthalic anhydride and *o*-tolylmagnesium bromide.[12] After the present work had been completed, Badger *et al.*[13] described a synthesis of pentaphene (VI) by cyclisation of 3:3-bisbromomethyl-2:2′-dinaphthyl, followed by dehydrogenation,[13] but this method did not give a higher yield than the earlier syntheses of Clar.[11,12] Reductive acetylation of (B) gave the tetra-acetate of the leuco compound. Interaction of (B) with hydrazine hydrate in boiling pyridine gave the reddish orange azaquinone (VII),[3,9] which dyed cotton a bright golden orange shade from a cherry-red vat. Reduction of (VII) with aluminium tri*cyclo*hexoxide gave the azahydrocarbon (VIII), lemon-yellow needles, m.p. 304°.

The carcinogenic properties of 3:4:9:10:dibenzopyrene (I) and 1:2-diaza-3:4:9:10-dibenzopyrene (VIII) are being examined at the Indian Cancer Research Centre. Subcutaneous injections of a ball-milled suspension of 2 mg of (I) or (VIII) in 0·2 ml of propylene glycol were given to sixteen mice; the hydrocarbon (I) produced the

(V)

(VI)



(VII)

(VIII)

first tumour after 90 days, and tumours developed in all the sixteen mice after 120 days; the azahydrocarbon (VIII) produced no definite tumour in 105 days, but a specific reaction at the site of injection was noticed in ten mice after 90 days.

Indanthrene scarlet 4G and Mayvat brilliant red AF dye substantially different shades and they exhibit different colours in sulphuric acid; the number and position of the halogen atoms, which must be responsible for these differences, are under investigation.

[11] E. Clar and Fr. John, *Ber. Dtsch. Chem. Ges.* **63,** 2967 (1930); *Ibid.* **64,** 981 (1931).
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EXPERIMENTAL

Purification and properties of Mayvat brilliant red AF

Mayvat brilliant red AF double paste (50 g) was dried at 110° for 4 hr and the reddish black powder (11 g) was dissolved in sulphuric acid (200 ml). The deep olive-green solution was poured into ice and water (1 l.), and the deep-red flocculent precipitate was collected, washed free from acid and dried (10 g). The chromatographic homogeneity of the dye was examined by dissolving 150 mg in molten naphthalene (50 g) and running the solution through a jacketed column of alumina (2·5 × 30 cm) maintained at 95–100°. Development with molten naphthalene produced a deep orange-red band, which was eluted with the same solvent. The naphthalene was removed by distillation and the dye was recovered as a red powder (120 mg), which crystallised from *o*-dichlorobenzene in red needles (Found: C, 60·3; H, 1·8; Cl, 2·4; Br, 28·1. $C_{24}H_{10}O_2Cl_{0\cdot3}Br_{1\cdot7}$ requires C, 60·4; H, 2·1; Cl, 2·2; Br, 28·5 per cent). The dye before chromatography also crystallised in red needles from *o*-dichlorobenzene (Found: C, 57·9; H, 2·4; Cl, 8·7; Br, 24·9. $C_{24}H_{10}O_2Cl_{1\cdot3}Br_{1\cdot6}$ requires C, 57·3; H, 2·0; Cl, 9·2; Br, 25·2 per cent). Indanthrene scarlet 4G crystallised from the same solvent in deep orange needles (Found: C, 53·6; H, 1·7; Cl, 15·3; Br, 24·5. $C_{24}H_{10}O_2Cl_{2\cdot4}Br_{1\cdot6}$ requires C, 53·2; H, 1·7; Cl, 15·6; Br, 23·8 per cent).

Cotton yarn dyed a 2 per cent shade with Mayvat red and Indanthrene scarlet 4G gives the following colour reactions:[14] (1) alkaline hydrosulphite: bluish red, red; (2) acid hydrosulphite: both yellow-brown; (3) concentrated nitric acid: rubine, scarlet; (4) concentrated sulphuric acid: black, deep rubine. Both Mayvat red and Indanthrene scarlet 4G dissolve in organic solvents such as *o*-dichlorobenzene or xylene to form orange solutions with a strong yellow fluorescence. The solution of Mayvat red in concentrated sulphuric acid is olive green and in 16 per cent oleum straw-yellow; Indanthrene scarlet gives a deep brownish red solution in concentrated sulphuric acid and a deep red solution in 16 per cent oleum.

Dehalogenation of Mayvat brilliant red AF

The finely powdered dye (1 g) was precipitated from sulphuric acid and washed free from acid. It was suspended in 5% sodium hydroxide solution (100 ml) in a pressure bottle, Raney nickel (1 g) was added, and the mixture was shaken with hydrogen at 38 lb pressure for 6 hr. The mixture was filtered, the nickel residue was washed with 2% sodium hydroxide solution containing a little glucose, and the combined deep-red filtrate was air-oxidised. The red precipitate was collected, washed and dried. The quinone (A; 0·58 g), which was halogen-free, crystallised from *o*-dichlorobenzene in deep red shining needles, m.p. 373° (Found: C, 85·9; H, 3·5. Calc. for $C_{24}H_{12}O_2$: C, 86·2; H, 3·6 per cent). The m.p. of 3:4:9:10-dibenzopyrene-5:8-quinone quoted in the literature[3] is 365°. This parent quinone, by the halogenation of which both Mayvat red and Indanthrene scarlet 4G are prepared, gives the same colourations as Mayvat red in *o*-dichlorobenzene, concentrated sulphuric acid and 16% oleum.

Reductive benzoylation of (A). The quinone (A) (50 mg) was shaken with 5% sodium hydroxide solution (20 ml) and sodium hydrosulphite (0·2 g) at 70–80° for

[14] H. B. Bradley and D. A. Derrett-Smith, *J. Soc. Dyers Col.* **56**, 97 (1940).

10 min. Benzoyl chloride (0·3 ml) was then added to the clear red vat and the mixture was shaken vigorously for 5 min, when a pale yellow granular precipitate separated (60 mg). Crystallisation from benzene gave pale-yellow needles, m.p. 343° (Found: C, 84·4; H, 4·1. $C_{38}H_{22}O_4$ requires C, 84·1; H, 4·0 per cent).

Reductive acetylation of (*A*). A mixture of the quinone (A) (100 mg), acetic anhydride (15 ml) and zinc dust (1 g) was heated under reflux for 2 hr and then filtered hot. The residue was extracted with hot acetic anhydride (10 ml) and the combined filtrates were concentrated to small bulk and poured into crushed ice with stirring. The precipitate (100 mg) crystallised from benzene in pale yellow needles, m.p. 310–15° (dec.) (Found: C, 79·7; H, 4·2. $C_{28}H_{18}O_4$ requires C, 80·3; H, 4·3 per cent).

Reduction of the quinone (*A*) *to* 3:4:9:10-*dibenzopyrene* (*I*). Aluminium turnings (1 g) were heated under reflux with *cyclo*hexanol (20 ml) after the addition of a few milligrams of mercuric chloride as catalyst. The quinone (A) (0·5 g) was added to the opalescent solution and the mixture was heated under reflux for 48 hr. *Cyclo*hexanol was removed by distillation and the pasty mass was stirred into 5% sodium hydroxide solution (200 ml). The last traces of *cyclo*hexanol were removed by steam-distillation, and the solution was then treated with sodium hydrosulphite (1 g) to dissolve any unconverted quinone. The mixture was filtered and the residual dark brown powder (0·7 g) was dissolved in warm benzene (250 ml) and chromatographed on alumina. The yellow fluorescent percolate was collected, concentrated to small bulk and cooled. Pale yellow plates of the hydrocarbon (I) were obtained (0·32 g). After recrystallisation from benzene–hexane the substance had m.p. 281° (Found: C, 94·9; H, 4·6. Calc. for $C_{24}H_{14}$. C, 95·4; H, 4·6 per cent). The hydrocarbon dissolves in benzene to an orange-yellow solution with a blue fluorescence. The solution in concentrated sulphuric acid is greenish blue, changing rapidly to blue and finally to violet; the solution first exhibits a blue fluorescence, which immediately changes to red, and disappears in a minute.

Scholl and Neumann[3] give m.p. 281·5–282°. Identity with 3:4:9:10-dibenzopyrene was proved by the absorption spectrum, which was identical with that recorded by Clar.[15]

Oxidation of the hydrocarbon (50 mg) by heating under reflux with chromic acid (500 mg) in water (10 ml) gave a product that crystallised from *o*-dichlorobenzene in red needles, m.p. 373°, alone or mixed with quinone (A) (Found: C, 86·6; H, 3·7. $C_{24}H_{12}O_2$ requires C, 86·2; H, 3·6 per cent).

Oxidation of quinone (*A*). The quinone (0·5 g) was heated under reflux with glacial acetic acid (20 ml), and a solution of chromic acid (2 g) in glacial acetic acid (20 ml) was added in five equal lots, each at the end of 8 hr. After the solution had been heated under reflux for 40 hr, it was diluted with water, and the yellow crystalline precipitate was collected, washed and dried (440 mg). Crystallisation from chlorobenzene gave yellow needles of quinone (B), m.p. 332° (Found: C, 78·3; H, 3·1. $C_{22}H_{10}O_4$ requires C, 78·1; H, 3·0 per cent). Scholl and Neumann[3] give m.p. 325° for pentaphene-5:14:8:13-diquinone (V). The substance gives an orange vat, which has no affinity for cotton. The solution in *o*-dichlorobenzene is yellow, and in concentrated sulphuric acid lemon-yellow.

Reductive acetylation of quinone (*B*). The quinone (B) (70 mg), acetic anhydride

[15] E. Clar, *Ber. Dtsch. Chem. Ges.* **69**, 1677 (1936).

(15 ml) and zinc dust (1 g) were heated under reflux for 2 hr and treated as described above. The product crystallised from benzene–hexane in pale yellow needles, m.p. 295–300° (dec.) (Found: C, 71·2; H, 4·2. $C_{30}H_{22}O_8$ requires C, 70·6; H, 4·3 per cent).

1:2-*Diaza*-3:4:9:10-*dibenzopyrene*-5:8-*quinone* (VII) *from quinone* (*B*). A mixture of quinone (B) (100 mg), 85% hydrazine hydrate (1 ml) and pyridine (10 ml) was heated under reflux for 1 hr. The mixture was diluted with water and aerated, and the orange-yellow precipitate was collected (100 mg). Crystallisation from *o*-dichlorobenzene gave reddish orange needles, m.p. above 360° (dec.) (Found: C, 79·0; H, 3·4; N, 8·7. Calc. for $C_{22}H_{10}O_2N_2$: C, 79·1; H, 3·0; N, 8·7 per cent). Scholl and Neumann[3] describe this compound as orange-red needles, decomposing ca. 440°. The substance dyes cotton an orange-yellow shade from a cherry-red vat.

Reduction of the azaquinone (VII) *to* 1:2-*diaza*-3:4:9:10-*dibenzopyrene* (VIII). On heating a mixture of the quinone (VII) (1 g) and a solution of aluminium turnings (1 g) in *cyclo*hexanol (20 ml) under reflux overnight and isolating the product as described above, an unvattable product (0·8 g) was obtained; after chromatography on alumina and crystallisation from benzene, the azahydrocarbon (VIII) was obtained as lemon-yellow needles (0·6 g), m.p. 304° (Found: C, 87·0; H, 4·2; N, 9·1. $C_{22}H_{12}N_2$ requires C, 86·8; H, 4·0; N, 9·2 per cent).

Reduction of quinone (*B*) *to pentaphene* (VI). Quinone (B) (0·2 g) was heated under reflux with a solution of aluminium turnings (0·5 g) in *cyclo*hexanol (10 ml) for 12 hr and the product was isolated as described above. Chromatography on alumina and crystallisation from benzene–hexane gave pale yellow needles (0·15 g), m.p. 262° (Clar and John[11] give m.p. 257° and Badger *et al.*[13] m.p. 255–257°) (Found: C, 94·8; H, 5·4. $C_{22}H_{14}$ requires C, 95·0; H, 5·0 per cent). The absorption spectrum of the hydrocarbon was determined in heptane solution, and was identical with that of pentaphene.[16] The substance dissolves in benzene to a very pale yellow solution with a blue fluorescence, and in concentrated sulphuric acid to a pale red solution on warming.

Dehalogenation of Indanthrene scarlet 4G

The purified dye (5 g) was dehalogenated by means of Raney nickel (3 g) and hydrogen at 40 lb pressure, as described for Mayvat brilliant red AF. The halogen-free quinone (3 g) crystallised from *o*-dichlorobenzene in red needles, m.p. 373°, undepressed by quinone (A) (Found: C, 86·0; H, 3·6. $C_{24}H_{12}O_2$ requires C, 86·2; H, 3·6 per cent). The quinone (0·3 g), on reduction with aluminium tri*cyclo*hexoxide (1 g of aluminium turnings in 20 ml of *cyclo*hexanol), gave the hydrocarbon (160 mg), pale yellow needles or plates from benzene–hexane mixture, m.p. 281°, undepressed by 3:4:9:10-dibenzopyrene prepared from Mayvat brilliant red AF (Found: C, 95·1; H, 4·5. $C_{24}H_{14}$ requires C, 95·4; H, 4·6 per cent).

Acknowledgements—This work was carried out under the auspices of the Council of Scientific and Industrial Research, to whom our thanks are due. We are indebted to the Otto B. May Co. Inc. and Cassella Farbwerke for gifts of dyes, and to Dr. T. S. Gore and Dr. G. D. Shah for the microanalyses recorded in the paper.

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ELECTROPHILIC SUBSTITUTION IN SKATOLE AND ITS DERIVATIVES

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(*Received* 18 *November* 1957)

Abstract—Evidence is presented to show that the 2-position is the primary site of electrophilic substitution in skatole and its derivatives. Existing data in the literature are reconciled with this view.

THE product from the strong acid-catalyzed reaction of skatole with benzaldehyde is formulated as 3,3′-dimethyl-2,2′-benzylidenebisindole (Ia).[1,2,3,4] This product was first assigned[5] the basic indolenine structure (II), although it is obtained in free form from strongly acidic solution. As recently as 1952, in an authoritative review,[6] the product was said "undoubtedly" to have structure (II). In agreement with structure (Ia), however, it was shown in 1948 that the product, as well as several closely related derivatives, have two hydrogen atoms that react instantly with a Grignard reagent.[3] Likewise, we find that structure (Ia) has NH < stretching absorption in the infrared region. Further, 1,3-dimethylindole forms a bisindole (Ib), analogous to (Ia), thus showing that an open 1-position is not required for bisindole formation. The ultraviolet spectra of (Ia) and (Ib) show typical indole absorption. They are compared in Table 1 with the spectrum of closely related 2-2′-dimethyl-3,3′-benzylidenebisindole

TABLE 1. ULTRAVIOLET ABSORPTION MAXIMA OF 3,3′-DIMETHYL-2,2′-BENZYLIDENEBISINDOLE AND RELATED COMPOUNDS

Compound	Wave lengths in 95% ethanol (mμ) and intensities (log ε)		
(Ia)	224 (4·82)	286 (4·31)	291 (4·29)
(Ib)	230 (4·84)	289 (4·29)	297 (4·27)
(III)	227 (4·79)	284 (4·15)	292 (4·10)
2,3-Dimethylindole	227 (4·79)[a]	283 (4·13)[a]	290 (4·08)[a]

[a] Log 2ε.

* Research Corporation research assistant, 1956–1957. We are indebted to the Research Corporation for a Frederick Gardner Cottrell grant in support of this research.

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[2] V. Dostál, *Chem. Listy* **32**, 13 (1938).
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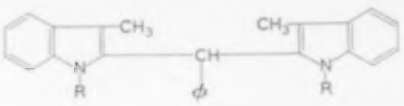
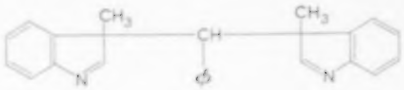
[5] M. Freund and G. Lebach, *Ber. Dtsch. Chem. Ges.* **38**, 2640 (1905).
[6] P. L. Julian, E. W. Meyer and H. C. Printy, *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 3, p. 95. Wiley, New York (1952).



I a, R = H
I b, R = CH_3



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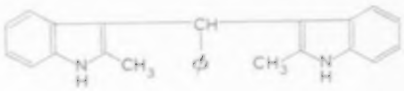
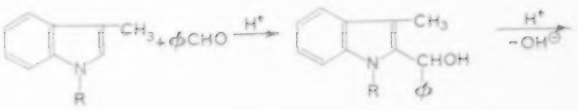
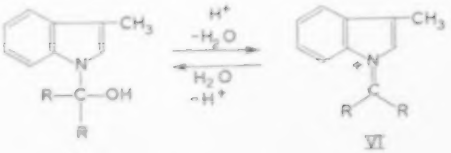


III



IV

I



V VI

(III). 2,3-Dimethylindole did not react with benzaldehyde under the conditions under which Ia was formed. All these facts support assignment of the 2-position as the point of attachment of the bridging carbon atom in (Ia) and (Ib). It would be expected that the 3-methyl group of skatole would activate the 2-position toward electrophilic substitution relative to the 2-position of indole in the same way as the methyl group of toluene activates the *o*- and *p*-positions relative to any position of benzene.

The mechanism of formation of bisindoles of type I probably involves an intermediate alcohol (IV). The isolation of a pale yellow amorphous substance, $C_{16}H_{15}NO$, corresponding in elemental analysis to (IV R = H), has been reported[7] from the reaction of skatole with benzaldehyde under conditions similar to those under which (Ia) is formed. Proof of structure for this possible intermediate appears, however, to be lacking.

The internal Mannich reaction suggested by Woodward[8] as a possible step in the biogenesis of strychnine involves electrophilic attack at the already occupied 3-position of tryptamine, while the 2-position remains open. It has been noted previously that this suggestion is still not illustrated by any model reaction.[4] In fact, all well authenticated examples of electrophilic carbon substitution in skatole and its derivatives appear to involve initial attack at the 2- and not at the 3-position.[3,4,9–12] Particularly pertinent in this regard is the internal Mannich reaction of *unsym.*-*N*-phenyl-*N*-skatylhydrazine and benzaldehyde, which has recently been reported to occur (92 per cent yield of crude product) with ring closure at the 2-position of the skatyl nucleus.[14] Consequently, we prefer Woodward's alternative suggestion[8] that in the biogenesis of strychnine preliminary oxidation of the 2-position of the indole nucleus might serve to force the initial attack into the 3-position.

In a series of interesting recent studies[10] of the condensation of skatole and its derivatives with 1,4-dicarbonyl compounds, it has been shown that ring closure occurs at the open 1- and 2-positions to yield benzpyrrocolines. The product from skatole and levulinic aldehyde was shown to be 1,8-dimethyl-2,3-benzpyrrocoline,[10] thus establishing that the more reactive aldehyde carbonyl group had attacked the 1-position of skatole. Consequently, it was proposed[15] that these 1,2-ring closures were initiated by attack on the nitrogen in the 1-position. This proposal can be reconciled with the fact that the 2-position in skatole is the usual point of electrophilic carbonyl attack if it is assumed that skatole (as well as other indoles having an open 1-position) and carbonyl compounds exist in a mobile, but generally unfavorable equilibrium with the corresponding amino alcohol (V) or the equivalent imine (VI). The formation of (V) or (VI) would give the levulinic aldehyde molecule a "beachhead" on the skatole nucleus from which the remaining carbonyl group could carry out the usual electrophilic attack on the 2-position in a sterically much more favorable environment (unimolecular) than would be possible under normal conditions (bimolecular) not involving ring closure.

With indole and 1,4-dicarbonyl compounds ring closure occurs first at the 3- and

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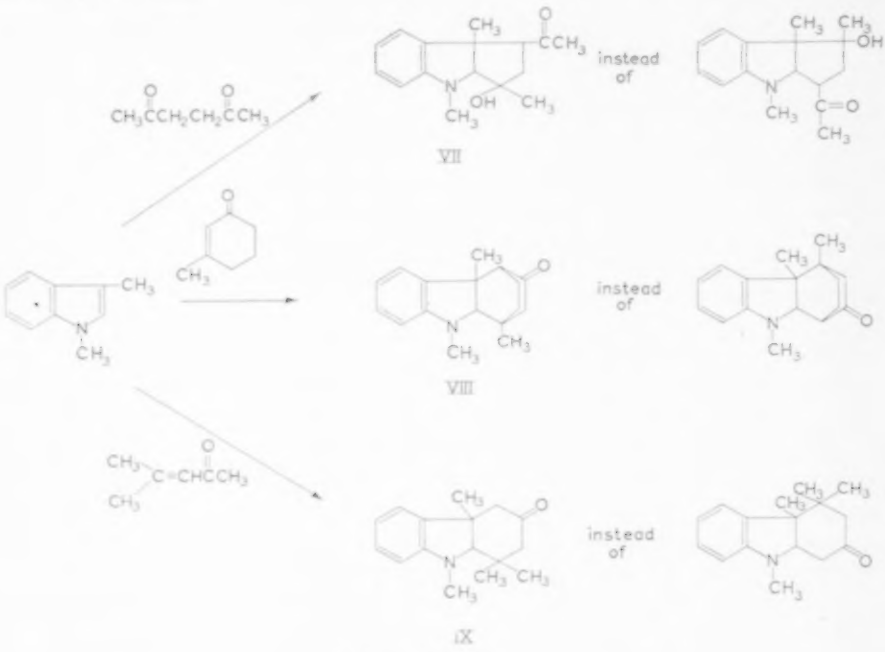
[13] J. Szmuszkovicz, *J. Amer. Chem. Soc.* **79**, 2819 (1957).
[14] J. Thesing and C. H. Willersinn, *Ber. Dtsch. Chem. Ges.* **89**, 1195 (1956).

then at the 2-positions, to yield the corresponding carbazoles.[10] With 1,3-dimethylindole ring closure also occurs at the 2- and 3-positions in condensations with hexane-2,5-dione or α,β-unsaturated ketones.[15,16] It was assumed that in these condensations with 1,3-dimethylindole initial electrophilic attack took place at the already occupied 3-position, with *subsequent* ring closure at the 2-position.[15,16] In keeping with the evidence cited in this paper it would appear more probable that the reverse order of attack is involved: initial electrophilic attack at the open 2-position, followed by ring closure at the already occupied 3-position. Consequently, the previously described[15,16] cyclization products having unsymmetrical structures may now have to be reformulated as (VII), (VIII) and (IX). These structures have additional attraction over the previous formulations because they do not involve the formation of bonds between quaternary carbon atoms, a process that would be expected to be quite sterically hindered.



VII VIII IX

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

3,3′-Dimethyl-2,2′-benzylidenebisindole (Ia)

This compound has been prepared previously from skatole and benzaldehyde, both in the presence of a small amount of zinc chloride[3,17,18] and in ethanol containing sulfuric[2] or hydrochloric[4] acids. In our hands three attempts with zinc chloride were unsuccessful, but (Ia) was obtained in 44 per cent yield, m.p. 159–161°, by the ethanolic sulfuric acid method.[2] Several recrystallizations from ethanol raised the m.p. to

[15] R. Robinson and J. E. Saxton, *J. Chem. Soc.* 2596 (1953).
[16] D. A. Cockerill, R. Robinson and J. E. Saxton, *J. Chem. Soc.* 4369 (1955).
[17] E. Fischer, *Ber. Dtsch. Chem. Ges.* **19**, 2988 (1886).
[18] M. Wenzing, *Liebigs Ann.* **239**, 239 (1887).

162–163°. Reported: 93 per cent, m.p. 161°.[2] ν_{NH} 3440 ($CHCl_3$), 3430 and 3380 cm^{-1} (Nujol).

1,3-*Dimethylindole**

The boron fluoride etherate–acetic acid method[19] was successfully applied to the Fischer indole synthesis of 1,3-dimethylindole[20,21] in 41 per cent yield, n_D^{25} 1·5882.

1,1′,3,3′-*Tetramethyl*-2,2′-*benzylidenebisindole* (Ib)

A mixture of 1,3-dimethylindole (7·3 g, 0·0502 mole), benzaldehyde (2·6 g, 0·0245 mole) and zinc chloride (2·0 g) was set aside overnight at room temperature. The red mixture, which was a precipitate mixed with the zinc chloride, was extracted with ether (100 ml) and the ether was evaporated. After standing overnight in the refrigerator, the red residue had deposited a mass of yellowish crystals (1·5 g, 0·0040 mole, 16 per cent), m.p. 200–203°. Several recrystallizations from acetone–water yielded colorless crystals, m.p. 207–209°. *Anal.* Calcd. for $C_{27}H_{26}N_2$ (378·49): C, 85·67; H, 6·92; N, 7·40. Found: C, 85·65; H, 6·98; N, 7·33.

Attempted reaction of 2,3-*dimethylindole with benzaldehyde*

By the method used for the preparation of (Ia),[2] 2,3-dimethylindole[19,22] (5·0 g, 0·0344 mole) and benzaldehyde (1·8 g, 0·0169 mole) were dissolved in ethanol (25 ml), concentrated sulfuric acid (17 drops) was added, and the solution was set aside overnight. No change in the appearance of the solution was noted and a strong odor of benzaldehyde remained. Dilution with water precipitated unreacted 2,3-dimethylindole in 93 per cent yield (after drying).

2,2′-*Dimethyl*-3,3′-*benzylidenebisindole* (III)

The preparation of this compound in unstated yield by warming 2-methylindole and benzaldehyde at 100° has been reported.[23]

2-Methylindole (2·0 g, 0·015 mole) and benzaldehyde (1·6 g, 0·015 mole) were mixed with glacial acetic acid (20 ml) and set aside. After a few minutes the solution turned red and colorless crystals were precipitated. After the solution had stood overnight, the crystals were collected and washed with ethanol (2·4 g, 0·0068 mole, 91 per cent), m.p. 248–251°. Two recrystallizations from acetone–water raised the m.p. to 252–255°. Reported m.p. 246–247° (uncorr.)[23] and 243°.[24] ν_{NH} 3480 ($CHCl_3$), 3400 cm^{-1} (Nujol).

* Experiment performed by John J. Baldwin.

[19] H. R. Snyder and C. W. Smith, *J. Amer. Chem. Soc.* **65**, 2452 (1943).
[20] J. Degen, *Liebigs Ann.* **236**, 162 (1886).
[21] L. Marion and C. W. Oldfield, *Canad. J. Res.* B **25**, 1 (1947).
[22] C. M. Atkinson, J. C. E. Simpson and A. Taylor, *J. Chem. Soc.* 165 (1954).
[23] E. Fischer, *Liebigs Ann.* **242**, 372 (1887).
[24] G. O. Burr and R. A. Gortner, *J. Amer. Chem. Soc.* **46**, 1224 (1924).

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N-METHYL DIHYDRONICOTINAMIDE

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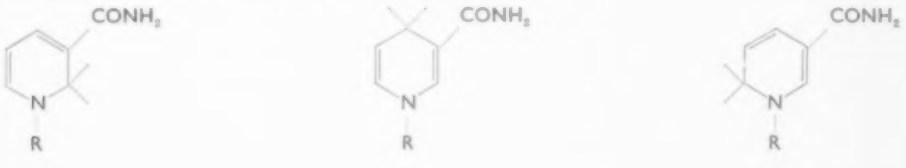
(*Received* 8 *November* 1957)

Abstract—The nuclear magnetic resonance spectra of N-methyldihydronicotinamide and of its 2-deutero and 6-deutero derivatives, amply confirm the 1,4-dihydropyridine structures assigned to these compounds.

IN 1936 Karrer and Warburg[1] made the important discovery that diphosphopyridine nucleotide (DPN^+) and triphosphopyridine nucleotide are reduced, during enzymatic reactions, in the pyridine ring. They also found that the same reduction can be accomplished with alkaline dithionite. At the time, they suggested that the reduction takes place in the 2-position of the pyridine ring, to produce the structure I, where R represents the adenine—ribose—pyrophosphate—ribose residue of DPN^+. Similar structures were suggested for models of reduced DPN, such as N-methyldihydronicotinamide,[2,3] which can be prepared by alkaline dithionite reduction of the corresponding quaternary salts of nicotinamide. However, following the discovery of direct hydrogen transfer (or deuterium transfer) in the enzymatic reactions[4] of DPN^+, Pullman, San Pietro and Colowick established that the reduction takes place in the 4-position[5] of the pyridine ring; their assignment was independently confirmed by Mauzerall and Westheimer,[6] who used a quite different method of establishing the structure. This latter method depended upon synthesizing 2-deutero-, 4-deutero-, and 6-deutero-nicotinamides, and demonstrating that in enzymatic[7] as well as in non-enzymatic model reactions[6] deuterium was transferred from the 4-position, and only from the 4-position, of the nicotinamide ring. The structure for reduced DPN and for a model compound (N-benzyl dihydronicotinamide) has therefore been firmly established as the 1,4-dihydro compound, II.



I II III

* Predoctoral Fellow, National Institutes of Health.

[1] P. Karrer and O. Warburg, *Biochem. Z.* **285**, 297 (1936).
[2] P. Karrer, G. Schwarzenbach, F. Benz and U. Solmssen, *Helv. Chim. Acta.* **19**, 811 (1936); P. Karrer and F. Blumer, *Ibid.* **30**, 1157 (1947).
[3] H. Kuhnis, W. Traber and P. Karrer, *Helv. Chim. Acta* **40**, 751 (1957).
[4] F. H. Westheimer, H. F. Fisher, E. E. Conn and B. Vennesland, *J. Amer. Chem. Soc.* **73**, 2403 (1951); B. Vennesland and F. H. Westheimer, *The Mechanism of Enzyme Action* (Edited by McElroy and Glass). Johns Hopkins Press, Baltimore (1954).
[5] M. Pullman, A. San Pietro and S. P. Colowick, *J. Biol. Chem.* **206**, 129 (1954).
[6] D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.* **77**, 2261 (1955).
[7] F. A. Loewus, B. Vennesland and D. L. Harris, *J. Amer. Chem. Soc.* **77**, 3391 (1955).

Nevertheless, Karrer and his collaborators have recently[3,8,9,10] repeated their assignment of a 1,2-dihydro structure to reduced DPN^+, on the basis of a set of analogies concerning the similarities and dissimilarities in the acid sensitivity of the model compounds with those of the Hantzsch compounds (i.e. of dihydropyridines which have a hydrogen atom rather than an alkyl group attached to the ring nitrogen atom). We have now determined the proton magnetic resonance spectra of N-methyldihydronicotinamide, N-methyldihydronicotinamide-2-D, N-methyldihydronicotinamide-6-D and of the dihydro compound obtained by reducing nicotinamide methiodide in D_2O. The results of these spectral observations amply confirm the assignment of the 1,4-dihydropyridine structure to these compounds.

EXPERIMENTAL

Materials: N-methyldihydronicotinamide was prepared according to the directions of Karrer and his co-workers[2,3,10] except that the compound was extracted from the aqueous reaction mixture with methylene chloride rather than with ether. The compound, crystallized from ethyl acetate, melted at 83·5–85·5° (evacuated capillary); λ_{max} 355 mμ ($\varepsilon = 6680$). Nicotinamide methochloride was reduced with dithionite in D_2O; the resulting dihydro compound (here identified as the 4-deutero derivative showed a m.p. of 85·3–86·8° (evacuated capillary); λ_{max} 355 ($\varepsilon = 6615$).

6-Deuteronicotinamide was prepared by the method reported previously;[6] its n.m.r. spectrum showed an almost complete lack of the peak assigned to the proton in the 6-position. The methiodide, on reduction in H_2O, gave the deuterated dihydro compound, m.p. 82–4° (evacuated capillary); λ_{max} 355 mμ ($\varepsilon = 6520$). 2-Deuteronicotinamide was prepared by the decarboxylation of quinolinic acid-D_2 and formation of the amide in a procedure paralleling that for 6-deuteronicotinamide.[6] Its n.m.r. spectrum completely lacked the peak assigned to the 2-proton in nicotinamide. The methiodide, on reduction, gave a deuterated dihydro compound, m.p. 81–3° (evacuated capillary); λ_{max} 355 mμ ($\varepsilon = 6615$). All of the dihydro compounds showed the characteristic[11] loss of ultraviolet absorption at 355 mμ and the development of a strong absorption at 298 mμ when their solutions were acidified. The deuterated compounds showed a low intensity band around 4·3 μ in the infrared region; this band was absent in the undeuterated compound.

Solutions (~50 per cent) of the dihydro compounds were prepared in D_2O (Stuart Oxygen Co.) or in acetone-D_6 (New England Nuclear Corp.; kindly donated by Dr. A. A. Bothner-By) and sealed in 5 mm tubes containing a sealed, *cyclo*hexane-filled reference capillary. The solutions in D_2O were specially prepared; to remove the proton absorption (resulting from an exchange of the amide protons with solvent) the dihydro compound was twice taken up in D_2O and lyophilized to dryness before final dissolution in D_2O for spectral examination. N.M.R. spectra, taken before each lyophilization, and an ultraviolet spectrum of the final solution demonstrated that the dihydro compound suffered only slight chemical change during this procedure. After 10 days in acetone-D_6, the N-methyl dihydronicotinamide-4-D, which had crystallized on cooling, showed a melting point of 83·0–85·5° and λ_{max} 355 mμ, $\varepsilon = 6560$. Another

[8] L. Kuss and P. Karrer, *Helv. Chim. Acta* **40**, 740 (1957).
[9] P. R. Brook and P. Karrer, *Liebigs Ann.* **605**, 1 (1957).
[10] P. Karrer, *A. Stoll Festschrift*. Basel (1957).
[11] P. Karrer, B. H. Ringier, J. Buchi, H. Fritzsche and U. Solmssen, *Helv. Chim. Acta* **20**, 55 (1937).

sample, all of which remained in solution, showed a λ_{max} 355, $\varepsilon = 5810$, indicating only slight decomposition after twenty days in this solvent.

Spectra. The n.m.r. spectra were observed at 40·01 Mc upon spinning samples, using a Varian Associates model V 4300 B Nuclear Magnetic Resonance spectrometer,

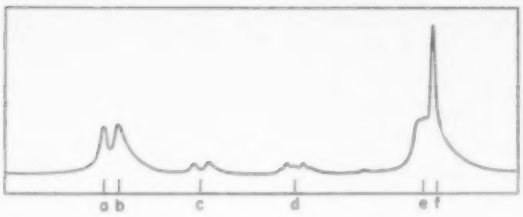


FIG. 1. N.M.R. spectrum of N-methyl-dihydronicotinamide in acetone-D_6. Displacements from the *cyclo*hexane line: *a*, 214 ± 1 c/s; *b*, 207 ± 1 c/s; *c*, 167 ± 1 c/s; *d*, 120 ± 1 c/s; *e*, 59 ± 2 c/s; *f*, 50 ± 2 c/s

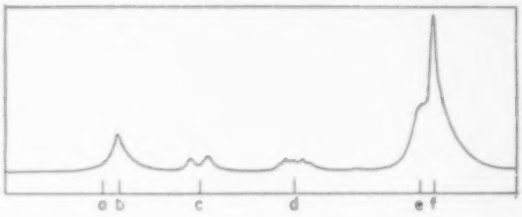


FIG. 2. N.M.R. spectrum of N-methyl-2-deuterodihydronicotinamide in acetone-D_6

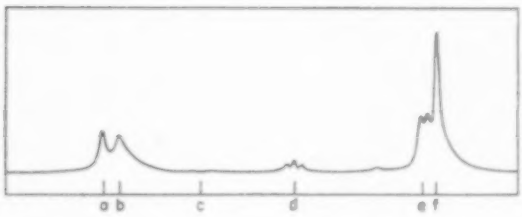


FIG. 3. N.M.R. spectrum of N-methyl-6-deuterodihydronicotinamide in acetone-D_6

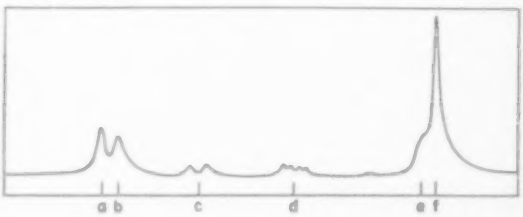


FIG. 4. N.M.R. spectrum in acetone-D_6 of the product obtained by reducing nicotinamide methiodide with dithionite in D_2O; product treated with water before solution in acetone-D_6

equipped with a "Superstabilizer". Line separations, measured by the side-band method,[12] and line positions, referred to the *cyclo*hexane absorption line, are accurate to ±1 c/s.

RESULTS AND DISCUSSION

The high-resolution spectrum for N-methyl dihydronicotinamide in acetone-D_6 is presented in Fig. 1. The spectra for the 2 and 6 deuterated compounds are presented in Figs. 2 and 3; the spectrum of the compound prepared by reduction of nicotinamide methiodide in D_2O is shown in Fig. 4. Since the spectrum (Fig. 4) of nicotinamide methiodide reduced in D_2O is not identical with either the spectrum of the 2-deutero

[12] J. T. Arnold and M. E. Packard, *J. Chem. Phys.* **19**, 1608 (1951).

or of the 6-deutero compound, the reduction product must be that of the 1,4-dihydro structure, II. The same conclusion can be reached independently by the more detailed consideration of the spectra given below.

The spectrum of N-methyldihydronicotinamide in D_2O is not shown, but is identical with that for this compound in acetone-D_6 except that the peak at *b* is totally missing; this experiment identifies this peak as that of the amide hydrogen atoms. The large peak at *f* is that of the N-methyl group, and the shoulder at *e* that of the methylene group. The very small peak, which appears between *d* and *e*, is almost absent in some preparations, and is presumably caused by a trace of impurity, probably water. The peak is greatly accentuated by the addition of water to the saturated solutions of the dihydro compound in acetone-D_6 and no peak was observed at this position (near 85 c/s) in freshly prepared samples in D_2O; in this solvent the H_2O peak is displaced to 120 c/s. At high resolution, we have been unable to obtain a quantitative relationship between peak area and the number of hydrogen atoms at a given position; the differentiation between one, two and three hydrogen atoms is, however, qualitatively clear.

A comparison of the spectra shows that the peak at *a* must be that of the hydrogen atom at position 2, since this peak is absent in the 2-deutero compound (Fig. 2), and the peak at *c* must be that of the hydrogen atom at position 6 since this peak is absent in the 6-deutero compound (Fig. 3). Structures I and III have methylene groups, rather than single hydrogen atoms, at positions 2 and 6 respectively. The n.m.r. spectra identify the peaks at *a* and *c* as those for single hydrogen atoms at positions 2 and 6, and therefore eliminate structures I and III from consideration. The identification of the reduction product as the 1,4-dihydro structure, II, is thus confirmed.

The above argument is strongly reinforced by the fine structure of the spectra. The peak at *a* in Fig. 1 (for the undeuterated N-methyldihydronicotinamide) can be identified, without reference to any other spectrum, as due to the hydrogen in position 2. The peak is not split, and is the only peak for a single hydrogen atom which is not split.* Only for the 2-hydrogen atom is there no adjacent hydrogen, and therefore the peak at *a* must correspond to this atom. This fact alone eliminates structure II from consideration, although (without other evidence) it does not eliminate structure III. This identification confirms that which was also made by an examination of the spectrum (Fig. 2) of the 2-deutero compound. This second identification of the peak corresponding to the hydrogen at position 2 is most important, because it shows conclusively that there has been no migration of deuterium from the 2-position during the preparation of the 2-deutero compound; Karrer[9,10] postulated such migrations to reconcile our data (and his own) with the hypothesis of the 1,2-dihydro structure. Since there has been no rearrangement in the preparation of the 2-deutero compound, a rearrangement in the preparation, by similar methods, of the 6-deutero compound becomes highly unlikely.

The rest of the fine structures are consistent with the assignment of structure. The

* Under still higher resolution than that here presented, peak *a* (and each peak of *c*) develops a partially resolved doublet structure ($J < 2$ c/s); such secondary splitting is of the magnitude observed for cross-ring interactions[12,14,15] and is considerably smaller than the primary splittings ($J = 9$ c/s). Furthermore, the secondary splitting of peak *a* is absent from the spectrum of the 6-deutero compound, and the corresponding splitting of each of the peaks of *c* is absent from the spectrum of the 2-deutero compound.

[13] *Technical Information Bulletin* Vol. 2, No. 1 Varian Associates, Palo Alto, Cal. (1957).
[14] R. Hutton, unpublished results.
[15] H. S. Gutowsky, C. H. Holm, A. Saika and G. A. Williams, *J. Amer. Chem. Soc.* **79**, 4596 (1957).

peak at *b* has already been identified as that of the NH_2 group. For N-methyldihydronicotinamide itself, the peak at *c* (previously identified as that of the hydrogen atom in position 6) is split into a doublet by the adjacent hydrogen atom at 5. The peak at *d* is that for the hydrogen atom at position 5, and has been split by the single hydrogen atom at 6 and the adjacent methylene group at 4 into a pair of partially-superimposed triplets.

The fine structure of the 2-deutero compound (Fig. 2) is essentially unchanged from that of the parent compound, in keeping with the fact that the 2-hydrogen atom is not adjacent to any other of the hydrogen atoms. The fine structure of the 6-deutero compound (Fig. 3) is changed in two respects: the peak at *d* (for the 5-hydrogen atom) which previously consisted of a pair of triplets, has now been simplified (since there is no hydrogen atom at position 6) to a triplet. Secondly, the expected splitting of the methylene group is now clear; it consists of a doublet produced by the interaction of the adjacent hydrogen atom in position 5. In the other spectra this splitting is not clear, perhaps because of a small cross-ring interaction[13,14,15] with the hydrogen atom at position 6.

The spectrum of N-methyldihydronicotinamide, obtained by reducing nicotinamide methiodide in D_2O, is shown in Fig. 4. The hydrogen atoms on the amide have been partially restored by solution in water prior to taking the spectrum. The shoulder at *e* has been diminished in size, since deuterium has been introduced, during reduction, at position 4, and the peak at *d* is a pair of doublets, split by the hydrogen atom at position 6 and the single hydrogen atom at position 4.

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SOME MECHANISMS OF OXIDATION

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Abstract—The Haber–Willstätter hypothesis of oxidation is criticised as having no proper theoretical basis, and its experimental support by Bartlett and Nozaki is shown to be invalid. The general adequacy of the classical view of oxidation primarily by electron transference is maintained by reference to oxidations of paraffins, olefins, alcohols, ethers, amines, aldehydes and ketones.

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WIELAND in 1912 inaugurated his studies of the formation of carbonyl from alcoholic groupings by catalytic removal of two hydrogen atoms.[1] Later he suggested that alcohol in the presence of "cellular catalysts" might yield the peroxy compound (I), from which either acetaldehyde or acetic acid could be derived:[2]

$$CH_3{\cdot}CH(O_2H)OH \rightarrow CH_3CHO + H_2O_2$$
$$CH_3{\cdot}CH(O_2H)OH \rightarrow CH_3CO_2H + H_2O$$

(I)

The nature of the initial activation process was not further specified, but Haber and Willstätter postulated the removal of a single hydrogen atom as the first step in the reaction:[3]

$$CH_3{\cdot}CH_2{\cdot}OH + \text{Enzyme} \rightarrow CH_3{\cdot}\dot{C}HOH + \text{Monodesoxyenzyme} + H^+$$

Similarly they assumed direct formation of the radical $CH_3\dot{C}O$ in the oxidation of acetaldehyde and also extended their hypothesis of single hydrogen abstraction to purely chemical processes. It has since been adopted as a basis of interpretation of numerous kinetic studies, and Haber and Willstätter's consideration of the strength of the —C—H bond has been supplemented by emphasis on the greater strength of the —O—H bond, in justification of their hypothesis in regard to alcohol.[4,5,6]

Evidently, however, the arbitrary limitation of determining influence on a reaction to one of the participants is inadmissible. Thus, although, in accordance with bond-strength considerations, Partington observed constancy of rate of thermal decomposition in a series of paraffin hydrocarbons,[7] this was disturbed by the presence of a second reactant, so that Cullis and Hinshelwood recorded considerable variation of induction period in the low-temperature oxidation of such hydrocarbons.[8] Further, consistent application of the bond-strength criterion would require rupture of a —C—C— rather than of a —C—H bond. Although this has in fact been assumed

[1] H. Wieland, *Ber. Dtsch. Chem. Ges.* **45**, 484, 2606 (1912).
[2] H. Wieland, *J. Chem. Soc.* 1055 (1931).
[3] F. Haber and R. Willstätter, *Ber. Dtsch. Chem. Ges.* **64**, 2844 (1931); cf. J. Kenner, *Ibid.* **65**, 705 (1932).
[4] J. L. Bolland and H. R. Cooper, *Proc. Roy. Soc.* A **225**, 405 (1954).
[5] C. F. Cullis and E. J. Newitt, *Proc. Roy. Soc.* A **237**, 540 (1956).
[6] K. M. Bell and C. H. Tipper, *Proc. Roy. Soc.* A **238**, 265 (1956).
[7] R. G. Partington, *Disc. Faraday Soc.* **2**, 114 (1947).
[8] C. F. Cullis and C. N. Hinshelwood, *Disc. Faraday Soc.* **2**, 116 (1947).

by Hinshelwood and co-workers to occur in the thermal decomposition of diethyl ether,[9–16] another interpretation of this reaction will be suggested as preferable. Finally, it is clear that the bond-strength concept offers no guidance as to the particular site of reaction in a given molecule. In fact, its introduction seems most unfortunately to have diverted attention from the fundamental fact that chemical, as well as extra-nuclear physical, phenomena are primarily electronic and not atomic in character.

Again, although Haber and Willstätter's equation recognised in respect of the enzyme the classical conception of oxidation as a process of electron transference, this was evidently only secondary to hydrogen transference. Also, owing to the virtually non-polar character of $\diagup\!\!\diagdown C—H$ bonds, the electron transference did not apply to the substrate; yet it is solely this aspect of the equation that has figured in the kinetic studies just mentioned. These have also been marked by neglect of any attempt to correlate their findings with either the relevant general data of chemistry or the classical electron-transference mechanism. In short, there has been consistent neglect of Occam's razor.

The photochemical oxidation of alcohol to acetaldehyde by excited benzophenone clearly involves electron transference, since the ketone is reduced to tetraphenylethylene glycol,[17] as is its unexcited form by metallic reagents. However, Bäckström noted an independent side-reaction in the presence of oxygen, which led to the formation of acetic acid, and so attributed his results to hydrogen abstraction[18] as envisaged by Haber and Willstätter. He did so the more readily since the formation of a mixture of di-,tri- and tetra-phenylethylene glycols by photolysis of a mixture of benzophenone and benzyl alcohol[19] clearly requires the formation of the two radicals $PhC\dot{H}OH$ and $Ph_2C\dot{O}H$. This is, however, consistent with an electron transference mechanism if isomerisation of benzyloxy (II) to phenylhydroxymethyl radical (III) be assumed:

$$Ph_2CO \xrightarrow{h\gamma} Ph_2\dot{C}—\dot{O}$$

$$Ph_2\dot{C}—\dot{O} + PhCH_2OH \longrightarrow Ph_2\dot{C}—\bar{O} + PhCH_2\dot{\overset{+}{O}}H$$

$$Ph_2\dot{C}—\bar{O} + PhCH_2\dot{\overset{+}{O}}H \longrightarrow Ph_2C\dot{O}H + PhCH_2O\cdot$$

$$PhCH_2O\cdot \longrightarrow PhC\dot{H}OH$$

(II) (III)

This change results in a condition of greater resonance and corresponds to that of triphenylmethoxy to diphenylphenoxymethyl radical[20]:

$$Ph_3CO\cdot \longrightarrow Ph_2\dot{C}OPh$$

[9] C. N. Hinshelwood, *Proc. Roy. Soc.* A **114**, 84 (1927).
[10] C. N. Hinshelwood and P. J. Askey, *Proc. Roy. Soc.* A **115**, 215 (1927).
[11] P. A. K. Clusius and C. N. Hinshelwood, *Proc. Roy. Soc.* A **128**, 82 (1930).
[12] J. V. S. Glass and C. N. Hinshelwood, *J. Chem. Soc.* 1804 (1929); *Ibid.* 1815 (1929).
[13] P. A. K. Clusius, *J. Chem. Soc.* 2607 (1930).
[14] L. A. K. Staveley and C. N. Hinshelwood, *Proc. Roy. Soc.* A **154**, 335 (1936); *Ibid.* **159**, 192 (1937); *J. Chem. Soc.* 1568 (1937).
[15] J. R. E. Smith and C. N. Hinshelwood, *Proc. Roy. Soc.* A **180**, 242 (1942); *Ibid.* **183**, 37 (1944).
[16] C. N. Hinshelwood, *The Structure of Physical Chemistry* p. 420. Oxford (1951).
[17] G. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.* **33**, 2911 (1900).
[18] H. L. J. Bäckström, *Svedberg Memorial Vol.* 456 (1944).
[19] W. D. Cohen, *Rec. Trav. Chim. Pays-Bas* **39**, 249 (1920).
[20] H. Wieland, *Ber. Dtsch. Chem. Ges.* **44**, 2550 (1911).

Similarly the trimethylene biradical, from electrolysis of potassium glutarate, at once isomerises to the more saturated propene[21]:

$$\bar{O}_2C(CH_2)_2\bar{C}O_2 \xrightarrow{-2e} 2CO_2 + [\cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot] \longrightarrow CH_2 \cdot CH = CH_2$$

These changes can be regarded as radical analogues of the Stevens rearrangement[22]:

$$\begin{array}{l} -\bar{C}H \cdot \overset{+}{N}Me_2 \\ \quad | \\ \quad CH_2Ph \end{array} \longrightarrow \begin{array}{l} -CH \cdot NMe_2 \\ \quad | \\ \quad CH_2Ph \end{array}$$

and illustrate the fact that, under a suitable impulse, radicals are liable to change like other electron-deficient systems. Thus radical disproportionation corresponds to the Hofmann degradation of organic kations:

$$\begin{array}{l} -CH_2 \cdot CH_2 \cdot \\ \cdot CH_2 \cdot CH_2 - \end{array} \longrightarrow -CH = CH_2 + H_2C \cdot CH_2 -$$

and the occurrence of Bäckström's side-reaction is attributable to a Wagner–Meerwein type of reaction of the positively charged hydroxyethyl radical (IV), resulting from attack of alcohol by excited benzophenone:

$$Ph_2\dot{C}{-}\dot{O} + CH_3 \cdot CH_2OH \longrightarrow Ph_2C\bar{O} + CH_3CH_2\overset{+}{\dot{O}}H$$

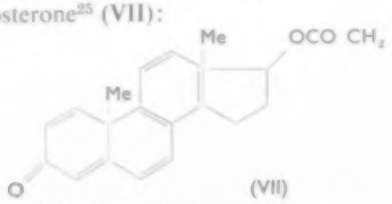
IV

$$CH_3 \cdot \overset{H}{\underset{O_2}{\overset{|}{C}}} H \cdot \overset{+}{\dot{O}}H \longrightarrow CH_3CH\overset{+}{O}H_2 \longrightarrow CH_3CHOH + \overset{+}{H}$$

Excitation of quinone also can induce oxidation of alcohol to acetaldehyde,[23] whilst direct photochemical oxidation of the alcohol by oxygen to acetic acid and acetaldehyde occurs in the presence of anthraquinone or its sodium 2:6-disulphonate.[4] The previous detailed discussion[24] of this reaction, in refutation of its interpretation by Bolland and Cooper, was based on the biradical (V), assumed by them as intermediate and derived by aromatisation of the excited state (VI) of the quinone, but is clearly also applicable to this latter, with its higher oxidation potential and correspondence to the excited state of benzophenone:

(V) (VI)

Further, the concordance of the effects of protonic and of photoactivation of 1-dehydro-*O*-acetyltestosterone[25] (VII):



(VII)

[21] B. L. Vanzetti, *Gazz. Chim. Ital.* **34** (II), 511 (1904).
[22] T. S. Stevens *et al.*, *J. Chem. Soc.* 2107, 2119 (1930); *Ibid.* 55, 69, 1926, 1932 (1932).
[23] G. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.* **34**, 1530 (1901).
[24] J. Kenner, *Nature, Lond.* **179**, 142 (1957).
[25] H. Dutler, H. Bosshard and O. Jeger, *Helv. Chim. Acta* **50**, 494 (1957).

supports the view that the effect of excitation is simply to increase the oxidation potential of ketones and quinones rather than to modify their normal electrophilic reactivity to one of hydrogen abstraction, as assumed by Bäckström and by Bolland and Cooper. Indeed, it would seem axiomatic that the effect of access of energy to a given molecular system can, so long as it remains intact and able to revert to its unexcited state, alter its reactivity only intensively and not qualitatively.

The limitation of oxidative changes in alcohol to the $\diagdown\!\!\diagup$CH— group adjoining the oxygen atom makes the probable participation of this as a source of electrons at once obvious. In the same way the oxidation of *iso*propyl alcohol by triphenylmethylsulphuric ester[26]:

$$Me_2C(OH)D + \overset{+}{C}Ph_3\cdot\overset{-}{S}O_4H \longrightarrow Me_2C{=}O + DCPh_3 + H_2SO_4$$

and similar reactions[26] also depend on electron transference from oxygen so that D is removed, not as atom, but as negatively charged ion. The analogous reaction with paraffins[27,28] constitutes the ionic counterpart of their attack by oxygen and by atomic chlorine:

$$EtMe_2CH + \overset{+}{C}Me_3 \rightleftharpoons EtMe_2\overset{+}{C} + HCMe_3$$

$$\diagdown\!\!\diagup CH + O_2 \longrightarrow \diagdown\!\!\diagup C\cdot + HO_2\cdot$$

$$\diagdown\!\!\diagup CH + Cl \longrightarrow \diagdown\!\!\diagup C\cdot + HCl$$

In these reactions the reagent, whether atom, oxygen or kation must be electrophilic, since it first encounters the electronic system enveloping an assemblage of carbon nuclei and protons and the susceptibility of the system to demand is well known, e.g. from the phenomena of aromatic substitution. Then the instability of kations $\overset{+}{R}H$, resulting from electron transference can induce a condition of hydrogen bonding leading to proton transference:

$$RH + X \longrightarrow \overset{\cdot+}{R}H + (\overline{e\text{-}X}) \longrightarrow R\text{-}(eX) \longrightarrow R\cdot + H(eX)\ *$$

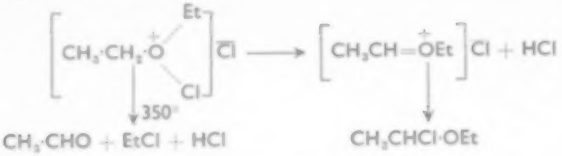
As already insisted, the hydrocarbon suffers no net electronic loss in this reaction and, for example, its oxidation only sets in when R· is attacked. Similar peripheral preliminaries must occur when radicals are employed, so that we have a further

* This scheme covers the anti-knock properties of 2:2:4-trimethylpentane. Thus, although the optimum region for attack surrounds C2, no hydrogen is available here for completion of the change. Again, although C4 carries a hydrogen atom the tertiary radical $Me_2C.CH_2\dot{C}Me_2$ resulting from attack should be relatively stable and experiment shows the corresponding olefin to be one product of oxidation of the pentane (F. F. Rust and Collamer, *J. Amer. Chem. Soc.* **76**, 1055 (1954)). The photodecomposition of paraffins, now well recognised as involving $\diagdown\!\!\diagup$C.H groups, is similarly attributable to preliminary ionisation to $\diagdown\!\!\diagup\overset{+}{C}H + e.$

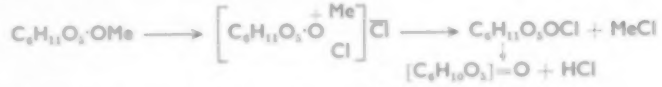
[26] P. D. Bartlett and J. D. McCollum, *J. Amer. Chem. Soc.* **78**, 1441 (1956).
[27] P. D. Bartlett, F. E. Condon and A. Schneider, *J. Amer. Chem. Soc.* **66**, 1531 (1944).
[28] H. Pines and R. Wacker, *J. Amer. Chem. Soc.* **68**, 593, 599 (1946).

illustration of the significance of electron deficiency for the chemistry of radicals. The sharp differentiation of these from carbonium ions, fostered by the terms homolysis and heterolysis, is artificial and unjustifiable in principle.

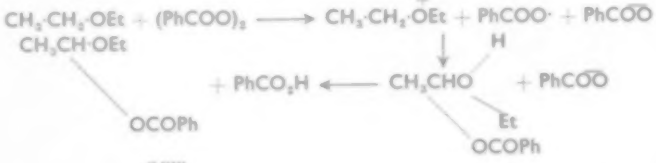
In ethers, as in alcohols, the oxygen atom is the seat of chemical reactivity. Thus the compound derived from ether by the action of chlorine at low temperature must be formulated[29] as $[Et_2\overset{+}{O}Cl]\overline{Cl}$. Under ordinary conditions this decomposes like other hypochlorites to yield chlorodiethyl ether[30] or, above 350°, acetaldehyde, ethyl and hydrogen chlorides[31]:



Similarly α-methylglucoside yields gluconolactone[32,33]:

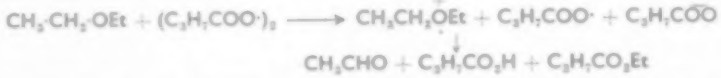


The benzoylation of ethers by benzoyl peroxide[34] can be written:



(VIII)

This formulation also covers the formation of ethyl *n*- and *iso*-butyrates by action of the respective peroxides on ether[35]:



Again, autoxidation of ether leads essentially to equimolecular proportions of acetaldehyde and hydrogen peroxide (or their compounds) together with some acetic acid and a small proportion of formic acid.[36,37,38] Its photochemical oxidation by quinones also corresponds to that of alcohol.[23] This correspondence supports the view that the primary occurrence in the oxidation of alcohol is one of electron transference and that the accompanying loss of proton is consequential. Similarly the reduction of silver oxide by acyl diazoethanes in the presence of aniline, preliminary to rearrangement,[39] shows it to be unnecessary to assume with Newman

[29] A. McIntosh, *J. Chem. Soc.* 789 (1905); O. Hassel, *Proc. Chem. Soc.* 250 (1957).
[30] O. Jacobsen, *Ber. Dtsch. Chem. Ges.* **4**, 215 (1871).
[31] H. P. Meissner and H. J. Schumacher, *Z. Phys. Chem.* A **185**, 457 (1940).
[32] A. Dyfverman, B. Lindberg and D. Wood, *Acta Chim. Scand.* **51**, 253 (1951).
[33] N. Lichtin and J. Saxe, *J. Amer. Chem. Soc.* **77**, 1875 (1955).
[34] W. E. Cass, *J. Amer. Chem. Soc.* **69**, 500 (1947).
[35] M. S. Kharasch, S. S. Kane and H. C. Brown, *J. Amer. Chem. Soc.* **63**, 526 (1941).
[36] H. King, *J. Chem. Soc.* 749 (1929).
[37] N. A. Milas, *J. Amer. Chem. Soc.* **53**, 221 (1931).
[38] E. J. Orloff, *J. Russ. Phys. Chem. Soc.* **40**, 799 (1908).
[39] G. Baddeley, G. Holt and J. Kenner, *Nature, Lond.* **163**, 766 (1941).

and Beal[40] that the first step in the reaction with corresponding derivatives of diazomethane consists in removal of proton.

The thermal disproportionation of ethers into carbonyl derivatives and paraffins constitutes an intramolecular process of oxidation and reduction:

Hinshelwood and his collaborators have expressed the results of their kinetic study of this reaction in the following adaptation to the case of diethyl ether of the scheme put forward by Rice and Herzfeld for dimethyl ether[41]:

$$CH_3{\cdot}CH_2{\cdot}O{\cdot}C_2H_5 \rightleftarrows {\cdot}CH_2{\cdot}O{\cdot}C_2H_5 + {\cdot}CH_3$$

$${\cdot}CH_3 + CH_3{\cdot}CH_2{\cdot}O{\cdot}C_2H_5 \rightleftarrows CH_3{\cdot}CH_3 + {\cdot}CH_2{\cdot}O{\cdot}C_2H_5$$

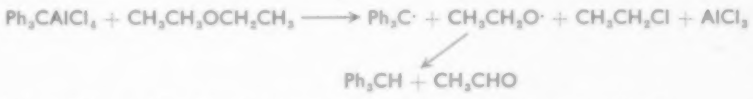
$${\cdot}CH_2{\cdot}O{\cdot}C_2H_5 \rightleftarrows {\cdot}CH_3 + CH_3{\cdot}CHO$$

$${\cdot}CH_3 + {\cdot}CH_2OC_2H_5 \rightleftarrows {\cdot}CH_3{\cdot}CH_2{\cdot}O{\cdot}C_2H_5$$

They emphasise that this accords with the doctrine of maximum simplicity, but it clearly offends Occam's razor, a special form of the doctrine, since it does not accord with the general behaviour of ether, as illustrated by the foregoing and by its decomposition by hydrogen iodide into ethyl alcohol and ethyl iodide:

$$EtOEt + HI \rightleftarrows E\,\overset{+}{\underset{H}{t}}OEt\ \bar{I} \rightarrow EtOH + EtI$$

In this reaction the alkyl iodide corresponds to the alkyl hydride of the thermal reaction. If, then, in place of a co-ordinative sharing of the electronic system of the oxygen atom with proton, an electron transference could be achieved, formation of carbonyl derivative rather than of alcohol should ensue. This in fact occurs when ether is added to a cold solution of triphenylmethyl aluminochloride[41]:



A similar reaction with chlorine above 350° has already been noticed.

Similarly (VIII) is the benxoyl derivative of acetaldehyde alcoholate. We thus conclude that, in all probability, the course of the thermal decomposition is similar, the determinant initial thermal effect being disturbance of the electronic system of the oxygen atom somewhat as follows:

$$CH_3{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_3 \overset{heat}{\rightleftarrows} CH_3{\cdot}CH_2{\cdot}\overset{+}{\underset{\cdot}{O}}{\cdot}CH_2{\cdot}CH_3 + e$$

$$\downarrow$$

$$CH_3{\cdot}CH_2{\cdot}O{\cdot} + {\cdot}CH_2CH_3$$

$$CH_3{\cdot}CH_2{\cdot}O{\cdot} \rightarrow H + CH_3CHO$$

$$H + CH_3{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_3 \rightarrow CH_3{\cdot}CH_2{\cdot}O{\cdot} + H{\cdot}CH_2{\cdot}CH_3$$

The particularly effective inhibitive action of nitric oxide is then expressed by the equations[42]:

$$CH_3{\cdot}CH_2{\cdot}O{\cdot} + {\cdot}NO \rightleftarrows CH_3{\cdot}CH_2{\cdot}O{\cdot}NO$$

$$CH_3{\cdot}CH_2{\cdot}O{\cdot}NO \rightarrow CH_3CHO + CH_3CH_2OH + NO$$

[40] M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.* **72**, 5163 (1950).
[41] F. O. Rice and K. H. Herzfeld, *J. Amer. Chem. Soc.* **56**, 287 (1934).
[42] J. F. Norris, *Organic Synthesis* (Coll. Vol. I) p. 532. Wiley, New York (1941).

whilst the catalytic action of large concentrations of the gas is attributable to the reaction:

$$EtOEt + NO \rightleftarrows EtO\cdot + EtNO$$

and that of hydrogen on low concentrations of the ether is perhaps due to the reaction:

$$EtOEt + H_2 \rightleftarrows EtO\cdot + H + ErH$$

Although the course of the decomposition of dimethyl ether is clear cut, that of diethyl ether is less so owing to some diversion by the reaction (cf. Kenner[34]):

$$CH_3{\cdot}CH_2{\cdot}O\cdot \rightarrow \cdot CH_3 + CH_2O$$

and its consequences.

The relationship of amines to alcohols and ethers renders their attack at the nitrogen atom by oxidising agents, e.g. chlorine, iodine, benzoyl peroxide[44] and acetyl peroxide[45], particularly significant for the present discussion:

$$Et_2NH + (PhCOO)_2 \rightarrow Et_2NOCOPh + PhCO_2H$$

$$2Ph_2NH + (CH_3COO)_{2\,2} \rightarrow Ph_2N{\cdot}NPh_2 + 2CH_3{\cdot}COOH$$

Kern[45] and Horner and co-workers[46] have also contributed studies of the behaviour of etheric and amino compounds, particularly of dimethylaniline, towards dibenzoyl peroxide in terms of electron transference. The adequacy of this standpoint in respect of the behaviour of aliphatic amines and ethers towards the peroxide was also recognised by Bartlett and Nozaki, but they gave preference to that of hydrogen abstraction because they did not observe the blue coloration characteristic of the tri-*p*-tolylaminium radical (X) during the reaction of benzoyl peroxide with tri-*p*-tolylamine (IX) in benzene solution.[47]

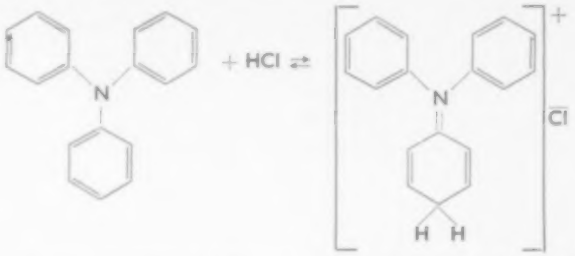
(IX)

(X)

However, the observations of Wieland and Wecker[48] and of Weitz and Schwechten[49] demonstrate the exceedingly slight tolerance of the radical ion for its positive charge. There can thus be little or no prospect of the existence of the ion in the presence of the anion of a weak acid like benzoic acid and still less if the radical $C_6H_5COO\cdot$ is also present. Further, the triarylamines are themselves completely devoid of basic properties, owing mainly to steric inhibition of a tetrahedral configuration round the nitrogen atom. The planar configuration thus imposed is, however, favourable to

[43] B. A. Gingras and W. A. Waters, *J. Chem. Soc.* 3508 (1954).
[44] St. Gambarjan, *Ber. Dtsch. Chem. Ges.* **42**, 4003 (1909); *Ibid.* **58B**, 1775 (1925); *Ibid.* **60B**, 390 (1927).
[45] W. Kern, *J. Makromol. Chem.* **1**, 209 (1948).
[46] L. Horner *et al.*, *Liebigs Ann.* **566**, 69 (1950); *Ibid.* **573**, 35 (1951); *Ibid.* **574**, 202, 212 (1951); *Ibid.* **579**, 175, 193 (1953); *Chem. Ber.* **85**, 804 (1952).
[47] P. D. Bartlett and K. Nozaki, *J. Amer. Chem. Soc.* **69**, 2299 (1947).
[48] H. Wieland and E. Wecker, *Ber. Dtsch. Chem. Ges.* **43**, 699 (1910).
[49] E. Weitz and H. Schwechten, *Ber. Dtsch. Chem. Ges.* **59**, 2307 (1926).

nuclear attack and these amines accordingly exhibit halochromy in benzene solution in the presence of hydrogen chloride; e.g.:



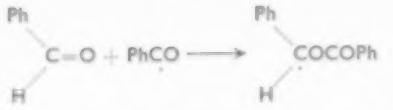
Similarly, no peroxide remained after a solution of tri-*p*-tolylamine (1·2 g) and benzoyl peroxide (4 g) in benzene (40 ml) had been boiled for 4 hr under reflux in a stream of nitrogen. After neutralisation with sodium hydroxide (18·6 ml) the separated benzene solution was evaporated. The filtered ethereal solution of the residue, after concentration and trituration with alcohol, yielded a vitreous product, apparently a mixture of isomeric tribenzoxy derivatives of tri-*p*-tolylamine [Found: C, 77·6; H, 5·37; N, 1·87. $C_{42}H_{33}O_6N_3$ (mol. wt. 675) requires C, 77·9; H, 5·1; N, 2·16 per cent]. It was easily hydrolysed by boiling alcoholic potassium hydroxide, (Calc. (OOC C_6H_5), 56·1. Found 56·0 per cent).

The assumption by Haber and Willstätter of the radical RCO as the first step in the autoxidation of aldehydes has been widely adopted. It accords with the suggestion by Bodländer[50] that perbenzoic acid is an intermediate product in the autoxidation of benzaldehyde and with the demonstration by Baeyer and Villiger that benzoic acid results from interaction of the peracid with benzaldehyde.[51] The numerous kinetic studies supplementing this observation have frequently been based on the Haber–Willstätter standpoint. Bawn and his collaborators[65,66] have, however, recently abandoned their original formulation on these lines in favour of a process of electron transference, but left its precise mechanism indeterminate.

Since, now, the oxygen atom is the negative pole of the carbonyl group and reactive towards proton, it should be so towards other electrophilic reagents, including radicals. This is experimentally confirmed by genesis of the dibenzoates of the stereoisomeric hydrobenzoins in the reaction of benzaldehyde with di-*tert.*-butyl peroxide.[67] The radical (XI) must be the precursor of the isomers and equally

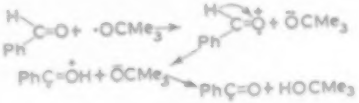
[50] G. Bodländer, *Ahrens Sammlung* **3**, 470 (1899).
[51] A. von Baeyer and V. Villiger, *Ber. Dtsch. Chem. Ges.* **33**, 858, 1560 (1900).
[52] M. Bodenstein, *Z. Phys. Chem.* **12B**, 151 (1931).
[53] M. Bodenstein, *Rec. Trav. Chem. Pays-Bas* **59**, 48 (1940).
[54] H. L. J. Bäckström, *Z. Phys. Chem.* **25B**, 115 (1934).
[55] H. L. J. Bäckström, *J. Amer. Chem. Soc.* **49**, 460 (1927).
[56] E. J. Bowen and E. L. Tietz, *J. Chem. Soc.* 234 (1930).
[57] H. J. Almquist and G. E. K. Branch, *J. Amer. Chem. Soc.* **54**, 2293 (1932).
[58] C. A. McDowell and J. H. Thomas, *J. Chem. Soc.* 2208, 2217 (1949); *Ibid.* 1462 (1950).
[59] J. B. Farmer and C. A. McDowell, *Trans. Faraday Soc.* **48**, 624 (1952).
[60] W. A. Waters and C. Wickham-Jones, *J. Chem. Soc.* 812 (1951); *Ibid.* 2420 (1952).
[61] J. R. Dunn, W. A. Waters and C. Wickham-Jones, *J. Chem. Soc.* 2427 (1952).
[62] R. F. Moore and W. A. Waters, *J. Chem. Soc.* 2432 (1952).
[63] H. R. Cooper and H. W. Melville, *J. Chem. Soc.* 1984, 1994 (1951).
[64] C. E. H. Bawn and J. B. Williamson, *Trans. Faraday Soc.* **47**, 721, 735 (1951).
[65] C. E. H. Bawn and J. E. Jolley, *Proc. Roy. Soc.* A **237**, 297 (1956).
[66] C. E. H. Bawn, T. P. Hobin and L. Raphael, *Proc. Roy. Soc.* A **237**, 313 (1956).
[67] F. F. Rust, F. H. Seubold and W. E. Vaughan, *J. Amer. Chem. Soc.* **70**, 3258 (1948).

must be derived from attack of the aldehyde through its oxygen atom by potential benzoyl radical:

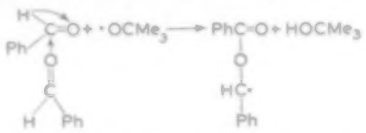


(XI)

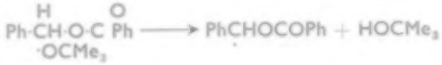
The occurrence of a similar attack of the aldehyde by *tert.*-butoxy radical (or by the methyl radical derived from it[68]) must then be accepted, and the formation of the benzoyl radical is readily expressed as the radical analogue of the Beckmann rearrangement:



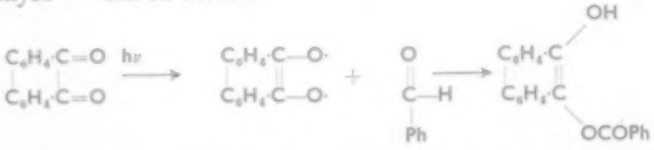
This analogy requires, however, that the migration of hydrogen be accompanied by simultaneous entry of a radical or its equivalent. The PhCO radical is thus probably not involved as a separate entity, and the correct representation of the reaction is as follows:



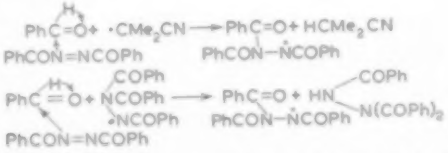
Mesoydrobenzoin is also formed by interaction of di-*t*-butyl peroxide and benzyl benzoate followed by dimerisation of a single form of (XI):



Similarly, the formation of phenanthryl benzoate from irradiated phenanthraquinone and benzaldehyde[69,70] can be written:



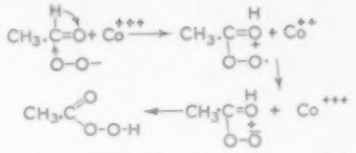
Again, the reaction of benzaldehyde with azobenzoyl, is promoted by the radical derived from azo*iso*butyronitrile:[71]



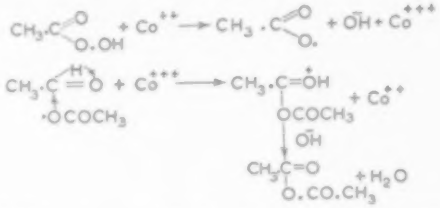
This presumably also applies to the corresponding reaction with ethyl azocarboxylate,[72] and the relationship of these azo compounds to oxygen[71] renders their reactions particularly relevant to the oxidation problem. Again, it is confirmatory of the

[68] N. A. Milas and D. M. Surgenor, *J. Amer. Chem. Soc.* **68**, 205 (1946).
[69] H. C. Klinger, *Liebigs Ann.* **249**, 143 (1888).
[70] R. F. Moore and W. A. Waters, *J. Chem. Soc.* 238 (1953).
[71] L. Horner and W. Naumann, *Liebigs Ann.* **587**, 81 (1954).
[72] K. Alder and T. Noble, *Ber. Dtsch. Chem. Ges.* **76**, 54 (1943).

foregoing interpretations of radical catalysis that cobaltic ion stimulates the autoxidation of acetaldehyde.[64] This reaction also can be represented without involving the free acyl radical, as follows:

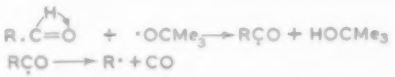


and the formation of acetic anhydride from acetaldehyde and peracetic acid, promoted by cobaltous ion, can be written:



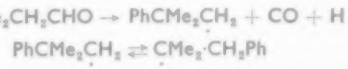
Corresponding formulations are applicable to retardation of benzaldehyde autoxidation by quinones (in biradical form), studied by Waters and his collaborators.[60,61,62]

The formation of (XI) is dependent on the resonance of the PhĊH— grouping. Failing it, and in absence of oxygen, the resonance of carbon monoxide determines breakdown of the acyl radical, so that butylperoxide provokes the chain decomposition of aliphatic aldehydes.[73]

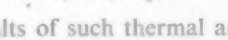


The recognised course of the subsequent reaction[74] can be similarly expressed:

The conversion of β-phenyl*iso*valeraldehyde by treatment with *tert.*-butyl peroxide into approximately equal proportions of *tert.*- and *iso*-butylbenzenes is due to migration of phenyl within the corresponding radicals.[75]



The small yields of the corresponding secondary alcohols occurring in these reactions would seem to be attributable to a reversal of the thermal decomposition of ketones followed by reduction:

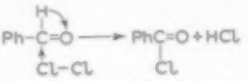


The correspondence of the results of such thermal and of photal with those of the above radical excitations indicates that the former also arise from a disturbance at the oxygen atoms, such as already suggested in the case of ether.

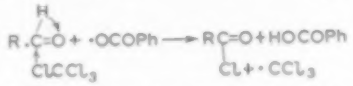
The formation of benzoyl chloride by chlorination of benzaldehyde[76] is the

[73] F. F. Rust, F. H. Seubold and W. E. Vaughan, *J. Amer. Chem. Soc.* **70**, 4253 (1948).
[74] J. A. Leermakers, *J. Amer. Chem. Soc.* **56**, 1537 (1934).
[75] S. Winstein and F. H. Seubold, *J. Amer. Chem. Soc.* **69**, 2916 (1947).
[76] L. Wöhler and H. von Liebig, *Liebigs Ann.* **3**, 262 (1832).

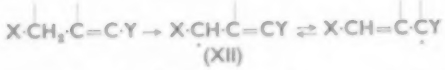
earliest recorded instance of apparent hydrogen abstraction, and is also satisfactorily explained in terms of preliminary attack on the oxygen atom:



Similarly for chlorination by carbon tetrachloride in the presence of benzoyl peroxide:

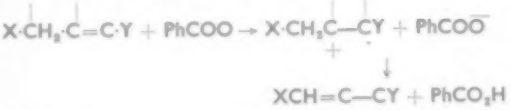


The α-oxidation of olefines depends on genesis of a mesomeric radical system (XII):

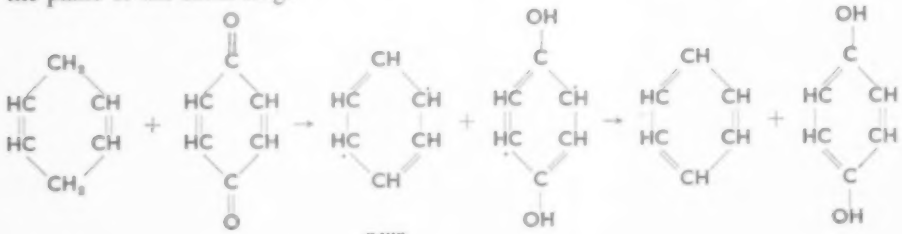


(XII)

and it is currently assumed that this arises from direct removal of a hydrogen atom.[77,78] This contravention of Occam's razor is the less acceptable since Kharasch, Engelmann and Mayo pointed out that the point of initial attack of olefines by atomic bromine is that carbon atom of the double bond with the greater electron availability.[79] Similarly propylene is more reactive towards atomic hydrogen than ethylene, and *iso*propyl predominates very largely over *n*-propyl radical in the product, whilst hydrogen abstraction is a very subordinate process.[80,81] The same would be expected of attack by a radical or of photochemical excitation. We then have a normal process of oxidation by electron transference, yielding radicals that combine with benzoxy radical to form the final product,[82] e.g.:



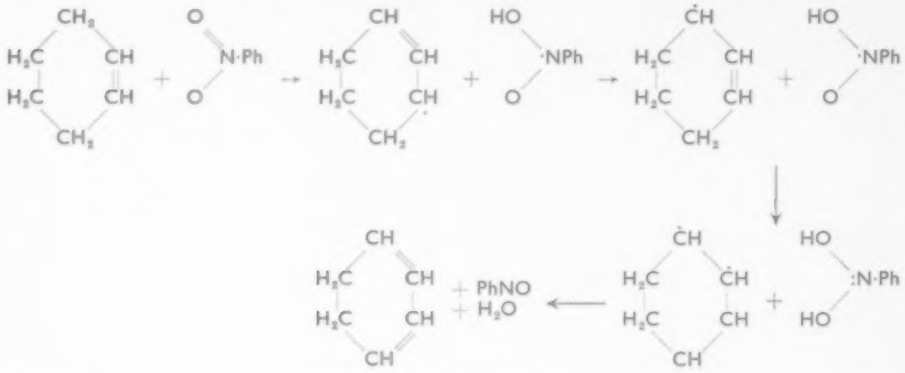
Experimental investigation of the reaction is complicated by chain polymerisation through the radical intermediate, but this is eliminated in the study of *cyclo*hexa-1:4-diene,[83] since the intermediate biradical (XIII) at once suffers aromatisation. The oxidation is ideally achieved by a molecule of quinone lying above and parallel to the plane of the diene ring:



(XIII)

[77] Cf. J. L. Bolland, *Quart. Rev.* **3**, 1 (1949).
[78] Cf. L. Bateman, *Quart. Rev.* **8**, 147 (1954).
[79] M. S. Kharasch, H. Engelmann and F. R. Mayo, *J. Org. Chem.* **2**, 288 (1937).
[80] J. N. Bradley, H. W. Melville and J. C. Robb, *Proc. Roy. Soc.* A **236**, 339, 455 (1936).
[81] B. de B. Darwent and R. Roberts, *Disc. Faraday Soc.* **14**, 55 (1953).
[82] Cf. E. H. Farmer, G. F. Bloomfield, A. Sundralingram and D. A. Sutton, *Trans. Faraday Soc.* **38**, 351 (1942).
[83] E. A. Braude, L. M. Jackman and R. P. Linstead *J. Chem. Soc.* 3548 (1954).

The reaction is favoured by polar solvents, proton activation and substitutional enhancement of the oxidation potential of quinone, but not by radical producing agencies. The unreactivity of *cyclo*hexa-1:3-diene is due to the unsuitable disposition of the seats of electron availability in the 1- and 4-positions in relation to the methylene groups. The initial stages of dehydrogenation of *cyclo*hexene by nitrobenzene in the presence of palladium[84] can be similarly represented with the plane of the nitro-group parallel to that of the olefinic system:



These several reactions thus conform to the respective general behaviours of olefines, quinones and nitro-compounds. A corresponding interpretation is applicable to the "allylic substitution" of olefines by maleic anhydride and by ethyl azocarboxylate[85,86,87,88] and the hypothesis of hydride-ion transference[84] should be discarded.

It will be seen that the catalogue of errors reviewed in the foregoing discussion derives not only from contravention of Occam's razor, but also from the fallacy that kinetic measurement can serve as a primary weapon of chemical investigation. The limitation of its legitimate use to that of a discriminant, auxiliary to purely chemical study, was accurately exemplified in the classical investigation of Lapworth,[89] which inaugurated the modern study of chemical mechanism.

[84] E. A. Braude, R. P. Linstead and K. R. H. Wooldridge, *J. Chem. Soc.* 3586 (1954).
[85] K. Alder, F. Pascher and A. Schmitz, *Ber. Dtsch. Chem. Ges.* **76**, 27 (1943).
[86] K. Alder and H. Söll, *Liebigs Ann.* **565**, 57 (1949).
[87] K. Alder and H. Söll, *Liebigs Ann.* **565**, 73 (1949).
[88] K. Alder and A. Schmitz, *Liebigs Ann.* **565**, 99 (1949).
[89] A. Lapworth, *J. Chem. Soc.* 30 (1904).

Tetrahedron, 1958, Vol. 3, pp. 90–91. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATIONS

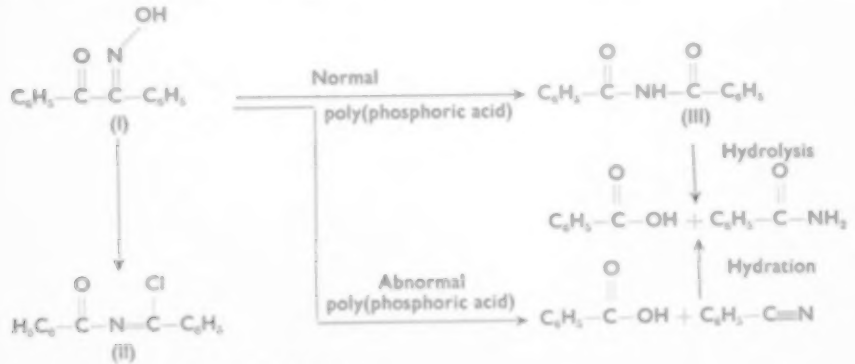
Abnormal Beckmann rearrangements in poly(phosphoric acid): benzil monoxime and benzoin monoxime

(*Received* 21 *November* 1957)

THE Beckmann rearrangements of benzil monoxime and benzoin monoxime have been the subject of extensive study.[1] Although the nature of the products has varied with the conditions of the reactions, in general, each monoxime has been shown in certain circumstances to yield products that could arise from an initial normal Beckmann rearrangement.[2] For example, the treatment of α-benzil monoxime (I) with phosphorus pentachloride in ether yields *N*-benzoylbenzimido chloride (II) which on hydrolysis yields ammonia and 2 molecules of benzoic acid.[3] Alternatively, Beckmann rearrangements of a monoxime of a diketone or an α-hydroxyketone, which may undergo a normal rearrangement under a variety of acid catalysts, can lead to an acid and a nitrile.[4,5] The treatment of α-benzil monoxime and α-benzoin oxime with benzenesulfonyl chloride in pyridine or in alkaline solution yields benzonitrile and benzoic acid, and benzaldehyde and benzonitrile, respectively. This reaction has been called a second-order Beckmann rearrangement or an abnormal Beckmann rearrangement.

It has been reported that poly(phosphoric acid) is the reagent of choice for the Beckmann rearrangement of compounds that might undergo an abnormal rearrangement.[6] As an example, the rearrangement of α-benzil monoxime to benzamide and benzoic acid in this medium was cited. Presumably these products were the result of a normal rearrangement followed by the hydrolysis of the imide (III) obtained. Recently, it has been observed that abnormal rearrangements do occur in poly(phosphoric acid)[7] and that nitriles are subject to hydration to the corresponding amide in this medium at the temperatures normally used to effect the Beckmann rearrangement.[8]

It was of interest, therefore, to re-investigate the rearrangement of benzil monoxime (and benzoin monoxime) in poly(phosphoric acid) in an effort to isolate the reaction intermediate (III) and thereby



[1] A. H. Blatt, *Chem. Rev.* **12**, 215 (1944).
[2] N. V. Sidgwick, *The Organic Chemistry of Nitrogen* (Revised and rewritten by T. W. J. Taylor and W. Baker) p. 182. Oxford University Press (1942).
[3] E. Beckmann and K. Sandel, *Liebigs Ann.* **296**, 280 (1897).
[4] A. Werner and A. Piguet, *Ber. Dtsch. Chem. Ges.* **37**, 4295 (1904).
[5] O. Diels and M. Stern, *Ber. Dtsch. Chem. Ges.* **40**, 1629 (1907).
[6] E. C. Horning, V. L. Stromberg and H. A. Lloyd, *J. Amer. Chem. Soc.* **74**, 5153 (1952).
[7] R. K. Hill and R. T. Conley, *Chem. & Ind. (Rev.)* 1314 (1956).
[8] R. T. Conley, Ph.D. Dissertation, Princeton University (1957).

establish the correct path of the transformation. The results of this study have shown that the rearrangement of α-benzil monoxime and α-benzoin monoxime in poly(phosphoric acid) follow an abnormal path rather than the normal rearrangement sequence previously postulated. By using reaction temperatures between 25 and 65°, it has been possible to show the presence of benzonitrile in yields of 15 to 70 per cent in the product mixture. None of the postulated imide intermediate (III) was observed. It was also possible to return the crude products, known to contain large amounts of the nitrile, to poly(phosphoric acid) and, after heating for 10 min at 110–115°, to isolate benzamide quantitatively along with an equivalent amount of benzoic acid.

Further substantiation of these results was obtained by the direct nitrosation of desoxybenzoin in poly(phosphoric acid). The nitroso compound so produced would be expected to rearrange to the oxime, which would undergo the abnormal Beckmann rearrangement *in situ*. These postulations have been substantiated by the isolation of high yields of the desired benzonitrile.

The rearrangement of α-benzoin monoxime yielded benzonitrile and benzaldehyde under similar treatment. It is quite clear, therefore, that these oximes undergo the abnormal Beckmann rearrangement in poly(phosphoric acid) rather than the normal rearrangement previously postulated.

Full experimental details of this work together with the rearrangements of related compounds will be submitted for publication shortly.

Acknowledgements—We express our gratitude to the Research Corporation for a Frederick Gardner Cottrell grant to support this and related research projects. We also wish to thank Professor R. K. Hill of Princeton University for his many comments and suggestions in connection with these investigations.

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Buffalo, New York

Zum Chemismus der Halogen–Lithium-Austauschreaktion

(*Received* 1 *February* 1958)

Der Austausch von Brom bzw. Jod gegen Lithium bei der Umsetzung von geeigneten Halogeniden mit lithium-organischen Verbindungen:

$$R—Hal + R'—Li \rightarrow R—Li + R'—Hal$$

wurde gleichzeitig (1938) und unabhängig von Gilman *et al.*[1] und Wittig *et al.*[2] entdeckt und seitdem in vielen Varianten bestätigt.[3] Aber noch ungeklärt blieb der Chemismus der präparativ wichtig gewordenen Methode.

Nach Wittig[4] wird dieser Platzwechsel dann begünstigt, wenn das Halogen durch induktive (oder u.U. mesomere) Effekte kationisch gelockert wird, wie das beim *o*-Brom-anisol der Fall ist. Bemerkenswert ist dabei die von uns immer wieder gemachte Beobachtung, dass die Austauschreaktion ausserordentlich rasch erfolgt. So führten Versuche,[5] die Reaktionsordnung des Vorganges zu ermitteln, nicht zum Ziel, da der Prozess auch bei 0° in nicht messbarer Zeit beendet ist.

Während eine Umsetzung über Ionen oder Radikale ausgeschlossen sein dürfte, zumal der Metall–Metall-Austausch ebenfalls rasch erfolgt, erscheint der Gedanke diskutabel, dass Halogen und Lithium über eine Anlagerungsverbindung der Partner ihre Plätze wechseln; denn derartige Addukte bilden sich nach den Erfahrungen aus der anorganischen Chemie her augenblicklich. Im

[1] H. Gilman, W. Langham und A. J. Jacoby, *J. Amer. Chem. Soc.* **61**, 106 (1939); *J. Org. Chem.* **3**, 108 (1938).
[2] G. Wittig, U. Pockels und H. Dröge, *Ber. Dtsch. Chem. Ges.* **71**, 1903 (1938).
[3] Vgl. R. G. Jones und H. Gilman, *Organic Reactions* (Bd. VI) S.339ff. Wiley, New York (1951)
[4] G. Wittig, *Naturwissenschaften* **30**, 701 (1942).
[5] E. Dietz, Dissertation, Universität Tübingen (1954).

Hinblick auf die ebenfalls momentan sich vollziehende metallorganische Komplexbildung,[6] z.B. zwischen Diphenyl-beryllium und Phenyl-lithium:

$$(C_6H_5)_2Be + C_6H_5{\cdot}Li \rightarrow [(C_6H_5)_2Be]Li$$

ist es naheliegend, die innerhalb einer Minute ablaufende Umsetzung von Benzylbromid und Phenyl-lithium zu Benzyl-lithium und Brombenzol im Sinne des folgenden Schemas zu formulieren:[7]

$$C_6H_5{\cdot}CH_2{\cdot}Br + C_6H_5{\cdot}Li \rightarrow \left[C_6H_5{\cdot}CH_2\overset{Br}{\underset{Li}{}}C_6H_5\right] \rightarrow C_6H_5{\cdot}CH_2{\cdot}Li + C_6H_5{\cdot}Br$$

(I)

Hiernach würde das Phenylanion (gegebenenfalls unter gleichzeitiger Bindung des Lithiumkations am Brom zum Komplex (I)) in die "weiche" Elektronenhülle des Bromliganden hineinstossen und unter vorübergehender *Ausweitung des Bromoktettes zum Dezett* das Benzylanion abdrängen, um sich schliesslich mit dem Bromkation zu Brombenzol zu vereinigen.[8]

Zur experimentellen Prüfung des Problems war das 1-*Brom-triptycen* (II) besonders geeignet, da sich diese Verbindung nach den ausgezeichneten Arbeiten von Bartlett *et al.*[9] wie analoge Bicyclen mit einem Brückenkopf-halogen[10] gegenüber anionischen Reagenzien indifferent verhält. Diese Passivität im Gegensatz zu der Reaktionsfreudigkeit des Tritylbromides ist darauf zurückzuführen, dass bei (II) dem substituierenden Agens der Zugang zum Brom-tragenden Kohlenstoff von der Rückseite her versperrt und ausserdem die zur Brom-Abspaltung notwendige Spreitung der anderen Liganden in die Ebene unmöglich gemacht ist. Wenn aber der Substitutionsakt am Brom im Sinne des oben postulierten Adduktes (I) erfolgte, sollte der Brom–Lithium-Austausch vonstatten gehen, sofern nicht auch hierbei eine komplanare Einstellung im Übergang* erst das Bromkation am 1-Kohlenstoffatom freigibt.

Bei der Umsetzung von Brom-triptycen mit Butyl-lithium in Äther–Benzol erfolgte nun ungehemmt die Austauschreaktion:

(II) (III)

zum *farblosen* (!) *Lithium-triptycen* (III), das bei der Hydrolyse *Triptycen* (III, H statt Li) in 69%iger Ausbeute lieferte. (III) bildete mit Kohlendioxyd die zugehörige *Triptycen-1-carbonsäure* (41%), die als solche und als Methylester charakterisiert wurde.

Die Befunde, die unsere Erwartungen bestätigten, legen nahe, dass beim Brom–Lithium-Austausch im Übergang ein kurzlebiges Intermediärprodukt entsprechend (I) entsteht, das im Energiediagramm durch eine Einbuchtung im Scheitel dokumentiert wird. Diese einer Energiesenkung entsprechende Gipfelwanne dürfte bei den Wasserstoff–Lithium-Austauschreaktionen—wenn überhaupt—nur angedeutet sein, da der Platzwechsel zwischen Protonen und Lithium-kationen entsprechend dem Schema:

$$R{-}H + R'{-}Li \rightarrow [R\cdots H\cdots R']^{\ominus}\,Li^{\oplus} \rightarrow R{-}Li + R'{-}H$$

(IV)

langsam erfolgt und beim Triptycen auch mit dem besonders wirksamen Diphenyl–lithium-natrium[11]

* Der übliche Terminus "Übergangszustand" sollte vermieden werden, da er eine contradictio in adjecto darstellt.

[6] Vgl. G. Wittig, *Angew. Chem.* **62**, 231ff (1950).
[7] G. Wittig und H. Witt, *Ber. Dtsch. Chem. Ges.* **74**, 1475 (1941); *Angew. Chem.* **70**, S. 66, Anm. 10 (1958).
[8] Eine derartige Schalenausweitung wurde beim Phosphor in geeigneten Verbindungen nachgewiesen: vgl. G. Wittig und K. Clauss, *Liebigs Ann.* **577**, 26 (1952); **578**, 136 (1953).
[9] P. D. Bartlett und H. Kwart, *J. Amer. Chem. Soc.* **72**, 1005 (1950); P. D. Bartlett und F. D. Greene, *J. Amer. Chem. Soc.* **76**, 1088 (1954).
[10] Vgl. D. E. Applequist und J. D. Roberts, *Chem. Rev.* **54**, 1065 (1954).
[11] G. Wittig und E. Benz, *Chem. Ber.* erscheint demnächst.

am 1-Kohlenstoffatom überhaupt nicht statthat. In diesen Fällen verdrängt das Kryptoanion $R'^{-\ominus}$ der metallorganischen Verbindung in einer Stoss-oder Zugreaktion im Sinne von (IV) ohne Haltepunkt die "schwächere Lewis-Base" $R^{-\ominus}$ aus ihrem Derivat RH.

Die Abwandlung des zugänglich gewordenen Triptycyl-lithiums zu naheliegenden Derivaten wird fortgeführt.

Chemisches Institut der
Universität Heidelberg

G. WITTIG
U. SCHÖLLKOPF

ERRATA

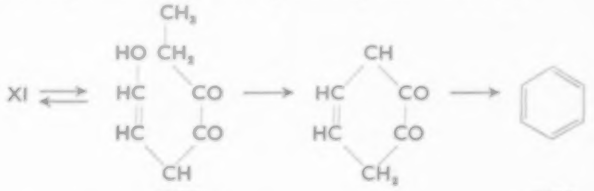
G. OCSKAY und L. VARGHA
Tetrahedron **2**, 140–150 (1958).

In line 25 on p. 142 the word "nicht" should be deleted, so that the sentence reads:

"Auf Grund dieser Experimente konnten wir die von uns hergestellten Furylketoximen in zwei Gruppen ordnen, von denen der umlagerbaren die *anti*-Furyl-Konfiguration zugeteilt wurde."

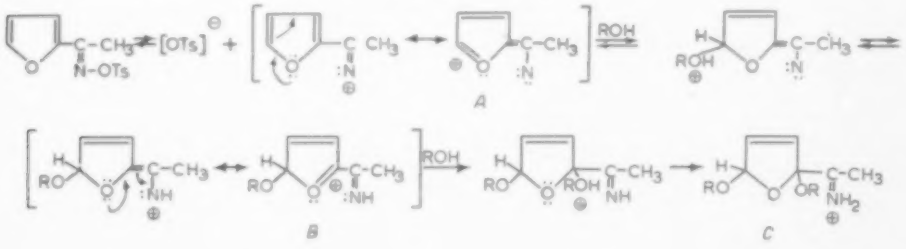
L. VARGHA und G. OCSKAY
Tetrahedron **2**, 151–163 (1958).

It is regretted that two errors occurred in the formulae of the above paper. The second equation on p. 153 should be replaced by the following:



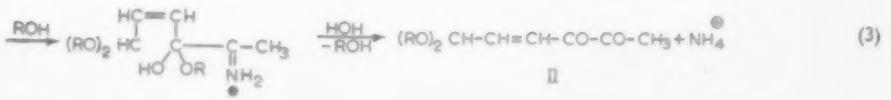
(XIII) (XIV)

The equation deleted from p. 153 should appear at the top of the second group of equations on p. 154. This complete group should then read:



A

B C



II (3)

Tetrahedron, 1958, Vol. 3, p. 94. Pergamon Press Ltd., London

BOOK REVIEW

Perspectives in Organic Chemistry (A commemorative volume dedicated to Sir ROBERT ROBINSON, O.M., F.R.S.) Edited by Sir ALEXANDER TODD, F.R.S. Interscience Publishers, New York and London, 1956. 525 pp., $7.50.

FROM time to time there appear men who in their lifetime dominate their chosen subjects, by intellect, vigour and personality. Such a man is Robert Robinson who has become the leader of organic chemistry, first in the United Kingdom and subsequently throughout the world. It is peculiarly fitting that this volume should have been dedicated to him on the occasion of his seventieth birthday which was celebrated last year. In it eighteen leading organic chemists, many of them his former pupils, have presented a fitting tribute to a unique figure. In his editorial foreword Professor Todd expresses the hope that the authors may have provided something which will be acceptable to Sir Robert and may also be of interest to organic chemists in general. We may suspect that they have hit their first target, they certainly have their second.

There is no lack today of collections of monographs on topics in organic chemistry. What makes the present one peculiarly attractive is that in it the authors have been encouraged to be philosophical, reflective and even speculative. As a result they have managed to escape from the curse of comprehensiveness which besets so much of our literature.

The names of the authors are a sufficient witness to their standing in their fields: Pauling on Resonance Theory; Bartlett on Mechanism; Wilson Baker on Aromaticity; Barton on Stereochemistry; Prelog on Many-membered Rings; Birch on Biosynthesis; Woodward on Synthesis; Zeigler on Organometallic Synthesis; Hirst on Carbohydrates; Todd on Nucleic Acids; Ruzicka on Terpenes; Shoppee on Steroids; Schlittler on Alkaloids; Cornforth on Isotopes; Folkers on Micro-organisms; Walker on Chemotherapy; Erdtman on Conifer Taxonomy and Butenandt on Organic Chemistry and Genetics.

Naturally the treatment of the subjects has varied greatly, from Ruzicka's scholarly fifty pages on the terpenes to Pauling's vigorous eight on resonance. In general the articles fall into two broad classes, the reflective essay and the informed review. Some of the authors have been unable to shake themselves entirely free from the shackles of detail and documentation but the general effect is one of great readability rising at its best to elegance. Four of the articles are in German, the rest in English.

Throughout the book runs a recurrent refrain—"It is no longer possible to think of organic chemistry and biochemistry as essentially different subjects".

A few of the essays may be specially mentioned. Bartlett's judicial review of mechanisms has a calm and balanced tone and looks forward agreeably into the region of biological systems. Erdtman's essay on organic chemistry and conifer taxonomy will probably open a new and fascinating world to many chemists. Cornforth on Isotopes, Folkers on Micro-organisms and Walker on Chemotherapy have brought together much valuable information in a readily assimilable form. A special delight is the essay on Synthesis, because of its mastery, its elegance of phrase and the introduction (on page 179) into the scientific literature of the word "serendipitous". It is indeed a far cry from Horace Walpole to R. B. Woodward, but the English language is capable of all things.

The editor, authors and publishers are to be warmly congratulated on their tribute, which is adorned by an excellent colour photograph of the man they have so appropriately honoured.

R. P. LINSTEAD

Papers to be published in future issues

D. H. WHIFFEN and D. STEELE: Carbon–hydrogen stretching vibrations in fluoro*cyclo*hexanes.

W. LANGENBECK: Über organische Katalysatoren—L. Entwicklungslinien der organischen Katalysatoren.

N. L. WENDLER, R. P. GRABER and G. G. HAZEN: The Favorskii rearrangement in the formation of 17-methyl steroids. The configuration of C-17 bromides.

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OXIDATIVE REACTIONS OF NITRILES—I

AUTOXIDATION*

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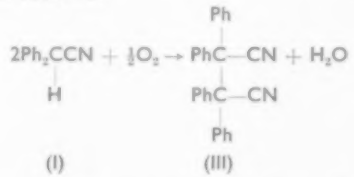
Abstract—It has been shown that, in the absence of any base, diphenylacetonitrile, *cyclo*hexylphenylacetonitrile and phenylacetonitrile do not react with oxygen. In the presence of a strong base, oxygen is slowly absorbed, and ketones or acids are formed in fair to excellent yields, depending upon the nitrile used. In the presence of a base and a trace of a copper salt a different reaction occurs. Excellent yields of tetraphenylsuccinonitrile are obtained from diphenylacetonitrile; methylphenylacetonitrile gives a poor yield of dimethyldiphenylsuccinonitrile; under comparable conditions *cyclo*hexylphenylacetonitrile, phenylacetonitrile and dimethylacetonitrile do not give dimers.

IN connection with the investigation of the mechanism of autoxidation, the reactions of a series of substituted acetonitriles with oxygen were thoroughly investigated. Solutions of diphenylacetonitrile (I) in pyridine, di*iso*propylamine, or di*cyclo*hexylamine do not absorb oxygen; the nitrile may be recovered. On the other hand, a solution of diphenylacetonitrile in freshly distilled piperidine slowly absorbs oxygen to give benzophenone (II) (yield 65 per cent) and a small amount of tetraphenylsuccinonitrile (III). Addition of small amounts of sodium methoxide to a piperidine solution of (I) causes a more rapid oxygen absorption and leads to the formation of the same products. Higher, but inconsistent, yields (18–44 per cent) of tetraphenylsuccinonitrile and correspondingly lower yields (60–40 per cent) of benzophenone are obtained when piperidine solutions of (I) are oxygenated in the presence of small amounts of benzyltrimethylammonium hydroxide (Triton B).

On the other hand, oxygen is readily absorbed when a small amount of cuprous or cupric bromide (1–2 mole per cent on the basis of nitrile used) is added to a solution of diphenylacetonitrile (I) in piperidine. Under these conditions, the oxygen absorption is complete within 3–10 min, instead of the 9–25 hr required when no copper salt is present. Since the yield of tetraphenylsuccinonitrile (III) is nearly quantitative, this reaction provides an excellent method for the preparation of (III). The stoicheiometry of the reaction is as follows:



In the presence of traces of copper salts, solutions of diphenylacetonitrile (I) in bases weaker than piperidine (di*iso*propylamine, diethylamine, or morpholine) absorb oxygen more slowly than do solutions of the nitrile in piperidine; relatively low yields

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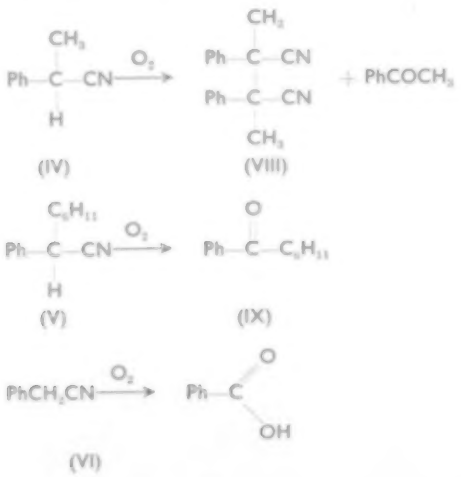
† Deceased.

(26–38 per cent) of tetraphenylsuccinonitrile (III) are obtained, along with benzophenone and unchanged starting material. However, in ethylenediamine solution the absorption of oxygen is rapid, and the yield of (III) is nearly quantitative. In the presence of inorganic bases (potassium hydroxide, sodium hydroxide or ammonium hydroxide) and copper salts, solutions of diphenylacetonitrile (I) in methanol rapidly absorb the calculated amount of oxygen; the yields of (III) are again nearly quantitative. It is, however, necessary to use an excess of the base; the optimum amount is 3–5 moles of base per mole of (I). In neutral media, oxidants such as potassium ferricyanide do not react with diphenylacetonitrile (I); but in basic media, the oxidation of (I) is rapid and excellent yields of (III) are obtained. In acetone, diphenylacetonitrile (I) reacts only slowly with potassium permanganate to give (III), but the reaction can be accelerated by addition of a base. In aqueous acetone, the reaction of potassium permanganate with (I) leads to the formation of benzophenone. The results of these experiments are shown in Table 1.

An ammoniacal solution of silver oxide in methanol is less effective than a similar solution of a copper salt as a catalyst for the autoxidation of diphenylacetonitrile; ferrous, nickelous, cobaltous and manganous salts are totally ineffective.

The autoxidations of methylphenylacetonitrile (IV), *cyclo*hexylphenylacetonitrile (V), phenylacetonitrile (VI) and dimethylacetonitrile (VII) in the presence of a base and of catalytic amounts of copper salts were also investigated. From methyl phenylacetonitrile (IV), a low yield (17 per cent) of dimethyldiphenylsuccinonitrile (VIII) was obtained, along with a large amount of acetophenone.* Under similar conditions, *cyclo*hexylphenylacetonitrile (V) gave only *cyclo*hexyl phenyl ketone (IX); phenylacetonitrile gave benzoic acid; and dimethylacetonitrile gave only traces of acetone, along with unchanged starting material.



DISCUSSION

In view of the fact that, in the absence of bases, nitriles do not react with oxygen,

* This reaction compares favorably with the method of preparation of (VIII) by the reaction of (IV) with iodine in a basic medium.[1]

[1] B. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **25**, 289 (1892).

TABLE 1.—OXIDATION OF DIPHENYLACETONITRILE AT ROOM TEMPERATURE

Ph_2CHCN	Solvent	Volume of solvent (ml)	Base*	Catalyst	Oxidant (moles/mole of nitrile)	Rate of oxygen absorption (ml/min)	Reaction products	
							TPSN† (per cent)	Ph_2CO (per cent)
0·02	methanol or pyridine	20	0·025 $NaOCH_3$ or Triton B	—	O_2(0·75–1·1)	340–490/540–720	0	90–100
0·02	piperidine	10	0·0002 $NaOCH_3$ or Triton B	—	O_2(0·70–0·95)	310–430/1500	20	50
0·01	piperidine	10	—	CuBr	O_2(ca. 0·25)	60/3	80	0
0·01	piperidine	10	—	$CuBr_2$	O_2(ca. 0·25)	70/10	95	0
0·01	*diiso*propylamine	20	—	CuBr	O_2(ca. 0·25)	60/30	40	‡
0·01	diethylamine	10	—	CuBr	O_2(ca. 0·25)	65/45	25	‡
0·01	diethylamine	10	—	CuBr	O_2(ca. 0·75)	155/120	10	70
0·01	morpholine	10	—	CuBr	O_2(ca. 0·25)	60/50	30	‡
0·005	ethylenediamine	5	—	CuBr	O_2(ca. 0·25)	25/25	80–95	0
0.005	methanol	10	0·0045 KOH	$CuBr_2$	O_2(ca. 0·25)	30/20	10	‡
0·005	methanol	10	0·027 $NaOCH_3$	$CuBr_2$	O_2(ca. 0·25)	30/15	95	0
0·005	methanol	40	0·4 NH_4OH	—	$CuBr_2(N_2)$(1·00)	—	45§	0
0·005	acetone	40	0·17 NH_4OH	—	$KMnO_4$(1·00)	(rapid)	90	0
0·005	acetone	40	—	—	$KMnO_4$(1·00)	(slow)	70	‡
0·005	acetone + water	40 + 5	—	—	$KMnO_4$(1·00)	(slow)	0	85§
0·005	methanol	40	—	—	$K_3Fe(CN)_6$(1·00)	—	0	0
0·005	methanol	40	0·25 NH_4OH	—	$K_3Fe(CN)_6$(1.00)	(rapid)	100	0

* Moles of base other than solvent.
† Tetraphenylsuccinonitrile.
‡ Product not isolated in this instance.
§ The yields were calculated on the reacted starting material in this case.

the results obtained with diphenylacetonitrile may be explained as follows:

$$Ph_2CHCN \xrightarrow{B^-} \underset{(X)}{Ph_2C{-}CN^{\ominus}} + HB \qquad (1)$$

$$(X) + Cu^{++} \longrightarrow \underset{(XI)}{Ph_2\dot{C}{-}CN} + Cu^{+} \qquad (2)$$

$$2(XI) \longrightarrow (III) \qquad (3)$$

In this formulation, cupric ion removes one electron from anion (X), and the function of oxygen is to regenerate the cupric ion. In fact, even in the absence of oxygen tetraphenylsuccinonitrile (III) is readily obtained from diphenylacetonitrile, if the stoicheiometric amount of a cupric salt is used. A similar explanation applies when the oxidant is a ferricyanide. It is interesting that, in this instance, even potassium permanganate serves as a one-electron oxidizing agent, since it, too, gives high yields of tetraphenylsuccinonitrile in alkaline solutions.

In the absence of copper salts, but in the presence of strong bases, diphenylacetonitrile (I) slowly absorbs oxygen to give benzophenone (II):

$$\underset{(X)}{Ph_2C{-}CN^-} + O_2 \longrightarrow \underset{\displaystyle O_2^{\ominus}\ (XII)}{Ph_2C{-}CN} \qquad (4)$$

$$(XII) \xrightarrow{NaOH} \underset{(II)}{Ph_2C{=}O} + HCN + [H_2O_2] \qquad (5)$$

Reactions (4) and (5), therefore, compete with reactions (2) and (3). Since the concentration of dissolved oxygen is rather low, reaction (2) may proceed more rapidly than reaction (4), because cuprous ions in basic solution are good oxygen "scavengers." With the other nitriles here mentioned reaction (2) is slow, because these compounds contain only one activating phenyl group; consequently, reaction (4) predominates. With methylphenylacetonitrile (IV), both reactions (2) and (4) take place, although at different rates, and symmetrical dimethyldiphenylsuccinonitrile (VIII) as well as acetophenone are formed. In other words, in the reactions of substituted acetonitriles with oxygen in the presence of catalysts the nature of the products formed depends on the nature of the substituents. These substituents determine (i) the ease of formation of the anion from the nitrile and (ii) the tendency of the anion thus formed to donate an electron to the catalyst.

EXPERIMENTAL

Autoxidation of diphenylacetonitrile (I)

(a) *In the presence of Triton B.* A solution of diphenylacetonitrile (3·86 g, 0·02 mole) and trimethylbenzylammonium hydroxide (Triton B, 0·0002 mole) in piperidine (20 ml) was stirred under an atmosphere of oxygen gas at room temperature. After 375 ml (0·015 mole) of oxygen had been absorbed (in about 25 hr), the reaction mixture was treated with ice–water, acidified with hydrochloric acid and extracted with ether. The ether was removed at reduced pressure, and light petroleum was added to the remaining oil. Crystals (0·58 g) slowly separated out; these were identified as unreacted diphenylacetonitrile. The oil was taken up in a small amount of benzene and chromatographed on a silica gel column, a mixture consisting of 80 per cent of

benzene and 20 per cent of light petroleum being used as eluent. Tetraphenylsuccinonitrile (0·77 g, 20 per cent) was eluted first. This was followed by unreacted diphenylacetonitrile, which was combined with the material previously recovered (0·85 g, 21 per cent). Finally, benzophenone (1·75 g, 49 per cent) was obtained. Alternatively, the reaction mixture could be separated by steam-distillation. The diphenylacetonitrile and benzophenone that distilled were separated by fractional crystallization from light petroleum. Tetraphenylsuccinonitrile was extracted from the residue with benzene and crystallized from glacial acetic acid. The tetraphenylsuccinonitrile thus obtained melted at 222–224° (dec.). *Anal.* Calcd. for $C_{28}H_{20}N_2$: C, 87·47; H, 5·24. Found: C, 87·30; H, 5·10 per cent.

(b) *In the presence of sodium methoxide.* Diphenylacetonitrile (3·86 g, 0·02 mole) was dissolved in a solution of sodium methoxide (0·027 mole) in methanol (55 ml). The solution was stirred under oxygen at room temperature and slightly above atmospheric pressure. After 12 hr, 335 ml (0·014 mole) of oxygen was absorbed. At this time, the rate of absorption decreased appreciably. On further addition of sodium methoxide (0·027 mole in 5 ml of methanol) no change in the rate of oxygen uptake was observed. The reaction mixture was poured into ice water, acidified and extracted with ether. After the ether had been removed by distillation, the residual oil (3·3 g 92 per cent) solidified. The solid was crystallized from light petroleum, m.p. 47°; the m.p. of a mixture with an authentic sample of benzophenone showed no depression.

(c) *In the presence of cuprous bromide.* To a solution of diphenylacetonitrile (0·97 g, 0·005 mole) in methanol (20 ml) was added a solution of cuprous bromide (0·02 g, 0·07 millimole) in concentrated ammonia solution (5 ml). The mixture was stirred under an atmosphere of oxygen, and the precipitation of tetraphenylsuccinonitrile commenced immediately. A total of 0·0025 moles of oxygen was absorbed. After the reaction mixture had been acidified, the product (0·90 g, 94 per cent) was collected on a filter and washed with small portions of methanol and ether. The tetraphenylsuccinonitrile thus obtained melted with decomposition at 220°.

Preparation of tetraphenylsuccinonitrile (III)

(a) *Oxidation of* (I) *with hydrogen peroxide and cuprous bromide.* To a well stirred mixture of diphenylacetonitrile (1·93 g, 0·01 mole) and cuprous bromide (0·02 g, 0·07 millimole) in piperidine (10 ml) under an atmosphere of nitrogen, hydrogen peroxide (10 ml of a 3% solution) was added. A precipitate formed immediately. The reaction mixture was stirred for a few minutes after the addition of hydrogen peroxide. The whole mixture was then poured into dilute hydrochloric acid, and the solid product was collected on a filter. The solid was washed first with water and then with methanol. Crude tetraphenylsuccinonitrile (1·4 g, 74 per cent) was thus obtained. After a single crystallization from acetic acid, the material melted with decomposition at 220°.

(b) *Oxidation of* (I) *with potassium ferricyanide.* To a solution of diphenylacetonitrile (0·97 g, 0·005 mole) in methanol (40 ml) was added a solution of potassium ferricyanide (1·7 g, 0·005 mole) in concentrated ammonia solution (15 ml). Tetraphenylsuccinonitrile (0·96 g), m.p. 220° (dec.), was recovered in the manner described above.

(c) *Oxidation of* (I) *with potassium permanganate.* Concentrated ammonia

solution (10 ml) was added to a solution of diphenylacetonitrile (0·97 g, 0·005 mole) and potassium permanganate (0·89 g, 0·005 mole) in acetone (40 ml). The reaction began at once, and manganese dioxide was deposited. After 30 min, the reaction mixture was acidified, and sodium hydrosulfite was added to reduce the manganese dioxide. Tetraphenylsuccinonitrile (0·86 g, 90 per cent), melting at 220° (dec.), was isolated from the reaction mixture.

(d) *Oxidation of* (I) *with* tert-*butyl hydroperoxide.* To a well stirred mixture of diphenylacetonitrile (1·93 g, 0·01 mole), cuprous bromide (0·1 g, 0·4 millimole) and piperidine (5 ml) under an atmosphere of nitrogen, *tert*-butyl hydroperoxide (0·02 mole) was slowly added. The resulting exothermic reaction was moderated by external cooling. The reaction mixture was then acidified. The solid (1·90 g, 98 per cent) which separated was collected on a filter, m.p. 220° (dec.); it was in all respects identical with an authentic sample of (III).

Methylphenylacetonitrile (IV)

The synthesis of (IV) was based on the procedure of Hancock and Cope[2] for the preparation of *cyclo*hexylphenylacetonitrile. This method gave a material purer than the products prepared by previously reported methods.[3,4,5] A few crystals of ferric nitrate were added to 200 ml of liquid ammonia contained in a Dewar flask. To the stirred solution sodium (8·1 g, 0·35 mole) was slowly added. When the reaction was complete, phenylacetonitrile (41 g, 0·31 mole) was added over a period of 15 min; stirring was continued for another 15 min. After the addition of dry benzene (200 ml), and ether (25 ml) the mixture was allowed to warm slowly to 0–5°. The mixture was then transferred by suction into a flask fitted with a condenser protected by a soda-lime drying tube. The Dewar flask was rinsed several times with ether, and the washings were transferred to the new reaction vessel. Ammonia and most of the ether were removed by gentle warming, with the aid of a stream of nitrogen. The reaction mixture was then cooled, and methyl iodide (70 g, 0·5 mole) was slowly added. External cooling was necessary to control the exothermic reaction. After the addition of methyl iodide, the mixture was heated under reflux for 3 hr. When the mixture had cooled, it was poured into ice–water. The layers were separated, and the aqueous layer was washed with benzene. The benzene solutions were combined and dried; the solvent was removed by evaporation. Distillation of the residue yielded an oil (35 g, 77 per cent), b.p. 76–77°/3 mm, n_D^{20} 1·5288. The infrared spectrum of this compound showed the methyl band at 1380 cm^{-1}. *Anal.* Calcd. for C_9H_9N: C, 82·40; H, 6·92; N, 10·68. Found: C, 82·79; H, 7·19; N, 10·80 per cent.

Autoxidation of methylphenylacetonitrile (IV)

To a solution of methylphenylacetonitrile (2·6 g, 0·02 mole) in piperidine (10 ml), cuprous bromide (0·2 g, 0·07 millimole) was added, and the mixture was stirred under nitrogen at room temperature and atmospheric pressure. In 5 hr about 500 ml of oxygen was absorbed, and a white precipitate had formed. The reaction mixture was diluted with water and acidified. The solid was collected on a filter (0·45 g, 17 per cent) After crystallization from glacial acetic acid, the dimethyldiphenylsuccinonitrile

[2] E. M. Hancock and A. C. Cope, *Organic Synthesis* (Vol. 25) p. 25. Wiley, New York (1945)
[3] V. Meyer, *Ann. Liebigs* **250**, 118 (1889).
[4] R. Hastings and J. B. Cloke, *J. Amer. Chem. Soc.* **56**, 2136 (1934).
[5] J. V. Murray and J. B. Cloke, *J. Amer. Chem. Soc.* **68**, 126 (1946).

(VIII) obtained melted at 227°; the m.p. of a mixture with an authentic sample showed no depression. *Anal.* Calcd. for $C_{18}H_{16}N_2$: C, 83·04; H, 6·20; N, 10·76; mol. wt., 260. Found: C, 83·20; H, 6·48; N, 10·76 per cent; mol. wt., 261 (Rast method).

The filtrate was extracted with ether. After evaporation of the solvent, there remained an oil (2 g), b.p. 83°/4 mm. The infrared spectrum of this oil indicated the presence of both ketone and nitrile groups. A portion of the oil (0·1 g) was treated with 2,4-dinitrophenylhydrazine to give acetophenone 2,4-dinitrophenylhydrazone (0·14 g), m.p. 239–241°; the m.p. of a mixture with an authentic sample showed no depression. The yield of acetophenone (based on the hydrazone formed) was 56 per cent.

Oxidation of methylphenylacetonitrile by cupric acetate

Over a period of 3 hr a solution of cupric acetate monohydrate (2·0 g, 0·01 mole) in piperidine (40 ml) was added with stirring to methylphenylacetonitrile (1·31 g, 0·01 mole) dissolved in piperidine (10 ml) under an atmosphere of nitrogen. When the mixture was acidified, (VIII) (0·25 g, 11 per cent) was precipitated, and it was collected on a filter, m.p. 225–227°. Unreacted nitrile (IV) (1·0 g) was recovered from the filtrate.

Preparation of diphenyldimethylsuccinonitrile (VIII)

A solution of iodine (2·56 g, 0·01 mole) in ether (20 ml) was added slowly to a mixture of phenylmethylacetonitrile (2·62 g, 0·02 mole), sodium methoxide (from 1·0 g of sodium), and methanol (20 ml). The reaction mixture was set aside for 1 hr and was then diluted with water. The resulting precipitate (0·35 g, 14 per cent) was collected and crystallized from glacial acetic acid, m.p. 227–228°.

Autoxidation of cyclo*hexylphenylacetonitrile* (V)

*cyclo*Hexylphenylacetonitrile[2] (9·0 g, 0·045 mole) was dissolved in piperidine (30 ml) containing cuprous bromide (0·5 g, 0·18 millimole). The mixture was stirred under an atmosphere of oxygen. The resulting exothermic reaction was moderated by external cooling. In 1 hr about 1 mole of oxygen per mole of nitrile was absorbed. When the reaction mixture was treated as described above for the preceeding autoxidation experiment, an oil (8–9 g) was obtained. A portion of this oil (7·0 g) was separated into two main fractions by distillation at 4 mm through a spinning-band column:

(1) *cyclo*hexyl phenyl ketone (1·5 g, 20 per cent), b.p. 130–132°/4 mm, m.p. 53–54°. *Anal.* Calcd. for $C_{13}H_{16}O$: C, 82·95; H, 8·52; mol. wt., 188.

Found: C, 82·75; H, 8·94 per cent; mol. wt., 179 (cryoscopic method in benzene).

(2) recovered (V) (4·6 g), b.p. 148–151°, n_D^{20} 1·5301.

The yield of *cyclo*hexyl phenyl ketone varied in different experiments from 25 to 32 per cent; it was determined as the 2,4-dinitrophenylhydrazone, m.p. 196–198°. *Anal.*

Calcd. for $C_{19}H_{20}N_4O_4$: C, 61·94; H, 5·47.

Found: C, 62·14; H, 5·60 per cent.

Autoxidation of phenylacetonitrile

Phenylacetonitrile (7·0 g, 0·05 mole) and a solution of sodium methoxide (0·135 mole) in methanol (25 ml) were placed in a pressure vessel, and the mixture

was shaken under oxygen at a pressure of 30 lb/sq. in. Immediately an exothermic reaction set in, and the mixture became brown. The reaction vessel was immersed in cold water in order to maintain the mixture at room temperature. The calculated amount of oxygen (0·05 mole) was consumed in 3½ hr. The reaction mixture was then taken up in ether and extracted with aqueous sodium hydroxide. The alkaline extract, when acidified, gave benzoic acid (5·5 g, 75 per cent), m.p., 120–121°; the m.p. of a mixture with an authentic sample showed no depression.

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OXIDATIVE REACTIONS OF NITRILES—II

REACTIONS WITH *TERT.*-BUTYL HYDROPEROXIDE*

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Abstract—Diphenyl-, *cyclo*hexylphenyl- and methylphenyl-acetonitrile react with *tert.*-butyl hydroperoxide in the presence of cuprous ions at 80°. By this means, α-*tert.*-butylperoxydiphenyl-, α-*tert.*-butylperoxyphenyl*cyclo*hexyl- and α-*tert.*-butylperoxymethylphenyl-acetonitrile, respectively, were obtained in good to excellent yields. Under similar experimental conditions, phenylacetonitrile gave oxygen, benzoic acid, *tert.*-butyl benzoate and *tert.*-butyl perbenzoate. In the absence of copper catalyst little reaction was observed. Dimethylacetonitrile did not react with *tert.*-butyl hydroperoxide in the absence of copper catalyst at 80°; in the presence of cuprous ions, however, it catalyzed the decomposition of the hydroperoxide to give oxygen in quantitative yield.

IN Part I,[1] the autoxidation of some substituted acetonitriles in the presence of a base and a copper catalyst was discussed. The present work is an extension of these studies. It deals with the reactivity of these nitriles towards *tert.*-butyl hydroperoxide in the presence of cuprous salts.‡ The reaction of the nitriles with *tert.*-butyl hydroperoxide was conducted in an unreactive solvent, and the amount of diluent was such that the copper-catalyzed decomposition of *tert.*-butyl hydroperoxide to form oxygen was limited to 5–10 per cent.

It was found that in the absence of cuprous ions diphenylacetonitrile reacts only slightly with *tert.*-butyl hydroperoxide; the nitrile alone does not catalyze the decomposition of *tert.*-butyl hydroperoxide to form oxygen. However, when cuprous bromide was added and the reaction mixture was stirred for 108 hr at room temperature, a high yield of α-*tert.*-butylperoxydiphenylacetonitrile was formed. This reaction, when carried out at 80°, was complete within a few hours. When cobaltous 2-ethylhexoate was used instead of cuprous bromide, the reaction proceeded rapidly at room temperature; however, there was also a rapid decomposition of *tert.*-butyl hydroperoxide to form oxygen.

It has previously been reported[1] that dimethylacetonitrile does not react with certain oxidants under the conditions investigated. A solution of dimethylacetonitrile in benzene, when stirred with *tert.*-butyl hydroperoxide in the presence of cuprous bromide at room temperature, did not give a mixed peroxide; instead, oxygen was liberated in quantitative yield. On the other hand, only traces of oxygen were produced even at 80° in the absence of either the nitrile or cuprous bromide. At present, the most plausible explanation of this observation is that copper salts

* This investigation is supported by a grant from the Office of Naval Research, Project NR 005-319.
† Deceased.
‡ Replacement of active hydrogen atoms in organic molecules by peroxy groups has been studied by Kharasch and Fono.[2]

[1] M. S. Kharasch and G. Sosnovsky, *Tetrahedron*, **3**, 97 (1958).
[2] M. S. Kharasch and A. Fono, *J. Org. Chem.* **23**, 324 (1958).

are quite soluble in dimethylacetonitrile and related substances. As a consequence, much larger quantities of catalyst become available for the reaction. At high concentrations of the catalyst the side-reaction, decomposition of the hydroperoxide to form oxygen, is favored (see "Discussion"). This hypothesis is supported by the fact that, under similar reaction conditions, cobaltous 2-ethylhexoate, which is soluble in organic solvents, always causes formation of large amounts of oxygen.

In the presence of cuprous bromide *cyclo*hexylphenylacetonitrile reacts smoothly with *tert.*-butyl hydroperoxide to give the expected mixed peroxide. The purification of this compound presented some difficulties, because of its high boiling point even at pressures below 0·1 mm. Although the compound was repeatedly distilled before it was analyzed, the infrared spectrum showed a very weak absorption in the carbonyl region. It was therefore concluded that small quantities of *cyclo*hexylphenyl ketone may have been formed during the reaction.

Methylphenylacetonitrile gave, in addition to appreciable amounts of oxygen, α-*tert.*-butylperoxymethylphenylacetonitrile. However, the following by-products were also identified: *tert.*-butyl benzoate, *tert.*-butyl perbenzoate, benzoic acid and traces of acetophenone. The occurrence of the first three products may be attributed to the presence of small amounts of phenylacetonitrile in the starting material. The presence of acetophenone was probably due to the oxidation of methylphenylacetonitrile.

The infrared spectra of these mixed peroxides showed an unusual feature. The parent nitriles have a medium to strong absorption band at 2225 cm^{-1} but the peroxides show little or no absorption in that region. This phenomenon has been previously described by Kitson and Griffith.[3] As a rule, compounds with a nitrile group attached to a carbon atom carrying another electronegative group have only very weak or no absorption in the nitrile region.

Benzaldehyde reacted with *tert.*-butyl hydroperoxide in the presence of cuprous bromide to form *tert.*-butyl perbenzoate, benzoic acid and oxygen.

DISCUSSION

The formation of mixed peroxides may be explained by the following mechanism:

$$Cu^{+} + Bu^{t}OOH \rightarrow Bu^{t}O\cdot + Cu(OH)^{+} \quad (1)$$

$$Bu^{t}O\cdot + \underset{R'}{\overset{R}{\overset{|}{\underset{|}{C}}}}\!\!-\!\!\overset{H}{\overset{|}{}}\!\!-\!\!CN \rightarrow Bu^{t}OH + \underset{R'}{\overset{R}{\overset{|}{\underset{|}{C}}}}\!\!\cdot\!\!-\!\!CN \quad (2)$$

$$\underset{R'}{\overset{R}{\overset{|}{\underset{|}{C}}}}\!\!\cdot\!\!-\!\!CN + Bu^{t}OOH + Cu(OH)^{+} \rightarrow \underset{R'}{\overset{R}{\overset{|}{\underset{|}{C}}}}\!\!-\!\!CN\,(OOBu^{t}) + Cu^{+} + H_2O \quad (3)$$

This mechanism involves (1) the formation of *tert.*-butoxy radical, (2) the attack of *tert.*-butoxy radical on the nitrile to form the nitrile radical and (3) the reaction of the nitrile radical with another molecule of hydroperoxide and cupric ion to give

[3] R. E. Kitson and N. E. Griffith, *Analyt. Chem.* **24**, 334 (1952).

the peroxide and to regenerate the cuprous ion. Reaction (3) may be formulated in two different ways: (*a*) oxidation of *tert.*-butyl hydroperoxide by cupric ion to give a *tert.*-butylperoxy radical, followed by the combination of two radicals, or (*b*) formation of a complex between the nitrile radical and *tert.*-butyl hydroperoxide, followed by oxidation of the complex by cupric ion:

$$Bu^tOOH + Cu(OH)^+ \rightarrow Bu^tOO^\cdot + Cu^+ + H_2O$$

$$\begin{matrix} R \\ \diagdown \\ \dot{C}\text{—}CN \\ \diagup \\ R' \end{matrix} + Bu^tOO^\cdot \rightarrow \begin{matrix} R \\ \diagdown \\ C\text{—}CN \\ \diagup \\ R'\ OOBu^t \end{matrix} \qquad (3a)$$

$$\begin{matrix} R \\ \diagdown \\ \dot{C}\text{—}CN \\ \diagup \\ R' \end{matrix} + Bu^tOOH \rightarrow [complex]$$

$$[complex] + Cu(OH)^+ \rightarrow \begin{matrix} R \\ \diagdown \\ C\text{—}CN \\ \diagup \\ R'\ OOBu^t \end{matrix} + H_2O + Cu^+ \qquad (3b)$$

The competitive side-reactions are: (4) generation of *tert.*-butylperoxy radicals by the reaction of *tert.*-butoxy radical with the hydroperoxide, (5) oxidation of *tert.*-butylperoxy radical by cupric ion to give oxygen and (6) oxidation of the nitrile radical by cupric ion to give cyanohydrin.

$$Bu^tO^\cdot + Bu^tOOH \rightleftharpoons Bu^tOO^\cdot + Bu^tOH \qquad (4)$$

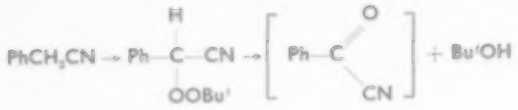
$$Bu^tOO^\cdot + Cu(OH)^+ \rightarrow Bu^tOH + Cu^+ + O_2 \qquad (5)$$

$$\begin{matrix} R \\ \diagdown \\ \dot{C}\text{—}CN \\ \diagup \\ R \end{matrix} + Cu(OH)^+ \rightarrow \begin{matrix} R \\ \diagdown \\ C\text{—}CN \\ \diagup \\ R'\ OH \end{matrix} + Cu^+ \qquad (6)$$

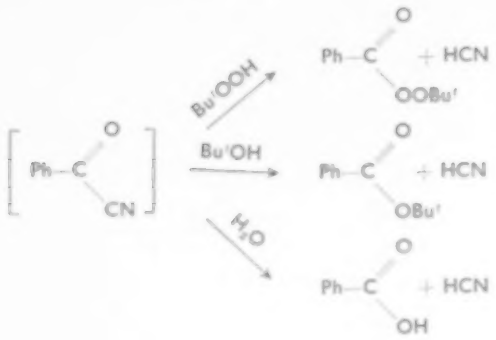
The mechanisms proposed for the side-reactions are supported by the fact that generation of oxygen is the main reaction when a nitrile of low reactivity (e.g., dimethylacetonitrile) is used or when the concentration of catalyst is high. Reactions (4) and (5) then become relatively more important than reaction (3). Ketones have been shown to be minor products when methylphenylacetonitrile and *cyclo*hexylphenylacetonitrile are used.

When phenylacetonitrile reacts with *tert.*-butyl hydroperoxide in the presence of cuprous bromide, the reaction products are: oxygen, benzoic acid, *tert.*-butyl benzoate, *tert.*-butyl perbenzoate, hydrocyanic acid and *tert.*-butyl alcohol. The ratio of *tert.*-butyl benzoate to *tert.*-butyl perbenzoate varies with the rate of addition of *tert.*-butyl hydroperoxide to phenylacetonitrile. When the two substances are mixed at once, about equal quantities of the two esters are formed; however, when *tert.*-butyl hydroperoxide is added gradually to phenylacetonitrile, formation of the benzoate is favored. In the absence of a copper catalyst only traces of these esters are formed. It has also been established that oxygen inhibits this reaction. Thus,

the yield of benzoic acid is reduced from 43 to 5 per cent by the presence of oxygen.



(7)



(8)

The mixed peroxide formed from phenylacetonitrile would be a secondary, and therefore unstable, peroxide,[4] which would be expected to decompose to form the hypothetical intermediate benzoyl cyanide. Benzoyl cyanide would react with *tert.*-butyl hydroperoxide (at high concentration) to give the perbenzoate; at low concentration *tert.*-butyl benzoate or benzoic acid would be formed. Inhibition of the reaction by molecular oxygen may be due to competition between oxygen and *tert.*-butyl hydroperoxide in the oxidation of cuprous to cupric ion. Here the extent of reaction (1) (as well as that of the subsequent reactions (2), (3), (7) and (8)) is diminished.

EXPERIMENTAL

α-tert-*Butylperoxydiphenylacetonitrile*

Method (a). A mixture of diphenylacetonitrile (9·7 g, 0·05 mole), *tert.*-butyl hydroperoxide (96 per cent purity, 10·8 g, 0·115 mole), cuprous bromide (0·25 g, 0·8 millimole) and benzene (200 ml) was heated under reflux for 3½ hr. Oxygen (200 ml, 13 per cent based on the hydroperoxide) was evolved. Cuprous bromide was removed by filtration, and the filtrate was concentrated at reduced pressure. The remaining oil (12 g, 86 per cent) solidified, m.p. 46–50°. A portion of this solid (1·55 g) was chromatographed on an alumina column, light petroleum being used as eluent. The compound recovered was α-*tert.*-butylperoxydiphenylacetonitrile (1·42 g, 79 per cent), m.p. 50–52°. A sample was recrystallized for analysis from light petroleum, m.p. 52·0–52·5°. *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76·84; H, 6·81; N, 4·98; mol. wt., 281. Found: C, 76·80; H, 6·82; N, 4·80 per cent; mol. wt., 268 (cryoscopic method in benzene). Infrared bands: 1385, 1365 cm^{-1} (*tert.*-butyl group); 755, 695 cm^{-1} (monosubstituted benzene); no band at 2250 cm^{-1} region.

Method (b). *tert.*-Butyl hydroperoxide (96 per cent purity, 23 g, 0·245 mole) in benzene (100 ml) was added with stirring over a period of 30 min to a mixture of diphenylacetonitrile (9·7 g, 0·05 mole), cobaltous 2-ethylhexoate (3 ml of a 15 per cent

[4] M. S. Kharasch, P. L. Pauson and W. Nudenberg, *J. Org. Chem.* **18**, 322 (1953).

solution in benzene, 0·0013 mole) and benzene (100 ml). An exothermic reaction began, and the temperature was kept at 25–30° by external cooling. After addition of the hydroperoxide, stirring was continued for 3 hr. During this period 1800 ml of oxygen was collected. Another portion of the hydroperoxide (23 g, 0·245 mole) in benzene (100 ml) was added during the next 30 min, and stirring was continued for a further 15 hr. A total volume of 4810 ml (0·213 mole, 87 per cent based on hydroperoxide) of oxygen was collected. A sufficient amount of alumina to decolorize the solution was added. The mixture was filtered, and the filtrate was concentrated at reduced pressure. The remaining oil (12·5 g, 90 per cent) upon standing crystallized, m.p. 50–52°.

Method (c). A mixture of diphenylacetonitrile (9·7 g, 0·05 mole), *tert.*-butyl hydroperoxide (98 per cent purity, 10·8 g, 0·115 mole), cuprous bromide (0·25 g, 0·8 millimole) and benzene (200 ml) was stirred at room temperature for 108 hr. By that time, all but a trace of the hydroperoxide had been consumed, and only 100 ml of oxygen had been formed. After removal of the catalyst and solvent, the remaining oil crystallized rapidly to a yellow solid, m.p. 46–48°. Recrystallization from light petroleum gave a white solid identical with α-*tert.*-butylperoxydiphenylacetonitrile isolated from previous experiments.

Method (d). When diphenylacetonitrile (9·7 g, 0·05 mole) and *tert.*-butyl hydroperoxide (96 per cent purity, 10·8 g, 0·115 mole) were heated under reflux for 6 hr, only a small amount of oxygen (140 ml) was evolved. Most of the peroxide (92 per cent) and diphenylacetonitrile (8·2 g, 84 per cent) were recovered. α-*tert.*-Butylperoxydiphenylacetonitrile (1·2 g, 9 per cent) was isolated from the remaining oil.

Reaction of tert.*-butyl hydroperoxide and dimethylacetonitrile in the presence of cuprous bromide*

When a mixture of dimethylacetonitrile (3·5 g, 0·05 mole), *tert.*-butyl hydroperoxide (96 per cent purity, 10·8 g, 0·115 mole) and cuprous bromide (0·1 g, 0·35 millimole) in benzene (100 ml) was stirred at room temperature for 8 hr, oxygen (0·05 mole) was evolved. The reaction mixture was distilled through a twenty-plate column. An azeotrope of benzene and *tert.*-butanol (21 g, containing 38 mole per cent of *tert.*-butanol)[5] b.p. 73–74° was collected. All the *tert.*-butanol formed during the reaction was thus accounted for. Successive fractions were composed of benzene, what appeared to be an azeotrope of benzene and dimethylacetonitrile, and dimethylacetonitrile.

In the absence of dimethylacetonitrile, it was found that at 80° and under comparable conditions only 10 per cent of the hydroperoxide was decomposed.

Reaction of phenylacetonitrile with tert.*-butyl hydroperoxide*

Method (a). A mixture of phenylacetonitrile (11·7 g, 0·1 mole), *tert.*-butyl hydroperoxide (96 per cent purity, 43 g, 0·46 mole) and cuprous bromide (0·1 g, 0·35 millimole) in benzene (340 ml) was heated under reflux for 7 hr. Oxygen (2350 ml, 46 per cent based on the peroxide used) was collected. The reaction mixture was extracted with 2 N sodium hydroxide to remove benzoic acid. The alkaline extract was acidified with hydrochloric acid, and the resulting precipitate of benzoic acid (4·5 g, 37 per cent)

[5] *International Critical Tables* (Vol. 3) p. 321. McGraw-Hill, New York (1933).

was collected and recrystallized from methanol, m.p. 121°; the m.p. of a mixture with an authentic sample showed no depression. The benzene solution was washed with water, dried over sodium sulphate, and concentrated at reduced pressure. The remaining oil had a boiling range of 50 to 110° at 5 mm of mercury. A portion of this oil (10·5 g) was fractionally distilled through a spinning-band column to give two main fractions:

(1) *tert.*-butyl benzoate (3·5 g, 23 per cent), b.p. 78–82/4 mm, n_D^{20} 1·4942. *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74·16; H, 7·86. Found: C, 74·13; H, 7·90. Infrared bands: identical with those of an authentic sample of *tert.*-butyl benzoate.

(2) *tert.*-butyl perbenzoate (2·8 g, 18 per cent), b.p. 87–90/2 mm, n_D^{20} 1·5012. *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68·50; H, 7·26; mol. wt., 194. Found: C, 68·40; H, 7·20; mol. wt., 187. Infrared bands: identical with those of an authentic sample of *tert.*-butyl perbenzoate.

Method (b). A mixture of phenylacetonitrile (24 g, 0·2 mole) and cuprous bromide (0·1 g, 0·35 millimole) in benzene (250 ml) was placed in a reaction flask equipped with a pressure-equalized dropping funnel. The flask was also connected through a condenser to a two-necked receiver. The receiver was equipped with a reflux condenser connected to a gas burette. The reaction flask was heated, and, when the distillation began, a solution of *tert.*-butyl hydroperoxide (96 per cent purity, 47 g, 0·5 mole) in benzene (250 ml) was added through the dropping funnel over a period of 2 hr. Benzene, *tert.*-butanol and water distilled into the receiver. Oxygen (1270 ml, 23 per cent based on hydroperoxide) was evolved. The distillate contained hydrogen cyanide (0·6 g). The reaction mixture was filtered and then concentrated at reduced pressure. The remaining oil was diluted with light petroleum and extracted with 2 N sodium hydroxide. The alkaline extract was acidified with hydrochloric acid, and the resulting precipitate of benzoic acid was collected (10·5 g, 43 per cent) and recrystallized from methanol, m.p. 121°; the m.p. of a mixture with an authentic sample showed no depression. The light petroleum solution was washed with water, and the solvent was removed at reduced pressure. The remaining oil (19 g) b.p. 65–95°/3 mm, n_D^{20} 1·5000, was fractionally distilled through a spinning-band column. The fractions were:

(1) *tert.*-butyl benzoate (8·6 g, 24 per cent), b.p. 75–78/3–4 mm, n_D^{20} 1·4940.

(2) *tert.*-butyl perbenzoate (2·7 g, 8 per cent), b.p. 90–92/2 mm, n_D^{20} 1·5010.

Method (c): *reaction in the presence of oxygen.* A mixture of phenylacetonitrile (11·7 g, 0·1 mole), *tert.*-butyl hydroperoxide (96 per cent purity, 24 g, 0·247 mole) and cuprous bromide (0·1 g, 0·35 millimole) was heated under reflux in an atmosphere of oxygen. After the usual treatment of the reaction mixture, *tert.*-butyl benzoate and perbenzoate and unreacted phenylacetonitrile were obtained. However, the amount of benzoic acid was much smaller (0·6 g, 5 per cent) than that obtained in the reaction from which oxygen was excluded.

Method (d): *in the absence of cuprous bromide.* A mixture of phenylacetonitrile (11·7 g, 0·1 mole) and *tert.*-butyl hydroperoxide (96 per cent purity, 24 g, 0·247 mole) in benzene (250 ml) was heated under reflux for 2½ hr. The benzene solution was concentrated at reduced pressure, and the remaining oil was fractionally distilled through a spinning-band column. This procedure gave only traces of *tert.*-butyl benzoate (1·1 g, 4 per cent) and *tert.*-butyl perbenzoate (0·2 g, 1 per cent), in addition to unchanged phenylacetonitrile (8 g, 67 per cent).

Reaction of tert.*-butyl hydroperoxide with benzaldehyde*

Method (a). A mixture of benzaldehyde (21·2 g, 0·2 mole) and cuprous bromide (0·1 g, 0·35 millimole) in benzene (250 ml) was stirred under an atmosphere of nitrogen. To this mixture, a solution of *tert.*-butyl hydroperoxide (96 per cent purity, 47 g, 0·5 mole) in benzene (250 ml) was added over a period of 2 hr. Oxygen (870 ml, 16 per cent based on the hydroperoxide used) was evolved. The benzene solution was extracted with 2 N sodium hydroxide to remove the copper salt and benzoic acid (10 g, 43 per cent), m.p. 121°, after recrystallization from methanol; the m.p. of a mixture with an authentic sample showed no depression. The benzene solution was concentrated at reduced pressure, and the remaining oil was distilled three times. The product recovered was *tert.*-butyl perbenzoate (6·5 g, 17 per cent), b.p. 104°/3–4 mm, n_D^{20} 1·5015. Infrared bands: identical with those of an authentic sample of *tert.*-butyl perbenzoate.

Method (b) When the *tert.*-butyl hydroperoxide was added in one portion, a similar result was obtained: oxygen (1320 ml); benzoic acid (17 g, 50 per cent); *tert.*-butyl perbenzoate (7·5 g, 19 per cent). No reaction was observed at room temperature.

α-tert-*Butylperoxy*cyclo*hexylphenylacetonitrile*

A mixture of *cyclo*hexylphenylacetonitrile (12·5 g, 0·063 mole) and cuprous bromide (0·1 g, 0·35 millimole) in benzene (250 ml) was heated under reflux. A solution of *tert.*-butyl hydroperoxide (96 per cent purity, 15·3 g, 0·16 mole) in benzene (200 ml) was added dropwise over a period of 2 hr. The reaction mixture was heated under reflux for another 5½ hr. Oxygen (580 ml) was collected. The reaction mixture was filtered, and the filtrate was concentrated at reduced pressure. The remaining oil (17 g) was distilled repeatedly for analysis. Efforts to purify the material by other means were unsuccessful. α-*tert.*-Butylperoxy*cyclo*hexylphenylacetonitrile, b.p. 107–108°/0·025 mm, n_D^{20} 1·5100. *Anal.* Calcd. for $C_{18}H_{25}O_2N$: C, 75·50; H, 8·76; N, 4·92. Found: C, 76·43; H, 8·44; N, 5·21. Infrared bands: 2220 cm^{-1} (just detectable, nitrile group); 1675 cm^{-1} (very weak, ketone group, probably *cyclo*hexyl phenyl ketone; 1390, 1365 cm^{-1} (*tert.*-butyl group).

α-tert.-*Butylperoxymethylphenylacetonitrile*

To a mixture of methylphenylacetonitrile[1] (13·1 g, 0·1 mole), cuprous bromide (0·1 g, 0·35 millimole) and benzene heated under reflux was added a solution of *tert.*-butyl hydroperoxide (96 per cent purity, 33 g, 0·34 mole) in benzene (220 ml) over a period of 6 hr. Oxygen (1720 ml, 44 per cent based on hydroperoxide) was collected. The reaction mixture was worked up in the usual manner to give an oil (17·5 g), b.p. 60–100°/3 mm, which was distilled through a spinning-band column. A number of fractions was collected; these fall in two groups:

(1) b.p. 70–74°/3 mm (3·7 g). This group of fractions was a mixture of several products. To judge from infrared analyses, refractive indexes and chemical properties, it appeared to consist of phenylacetonitrile (impurity in the starting material), methylphenylacetonitrile (ca. 14 per cent), *tert.*-butyl benzoate (6 per cent) and acetophenone (0·2 per cent, based on methylphenylacetonitrile; 2,4-dinitrophenylhydrazone, m.p. 237°).

(2) b.p. 97–99°/3 mm (9·3 g). This group of fractions consisted mainly of α-*tert.*-butylperoxymethylphenylacetonitrile (71 per cent). The first cuts (4·9 g)

were contaminated with benzoic acid (0·5 g) and traces of *tert.*-butyl perbenzoate. The last cuts (4·4 g, n_D^{20} 1·4853) were analytically pure. *Anal.* Calcd. for $C_{13}H_{17}NO_2$ C, 71·50; H, 7·78; N, 6·42; mol. wt., 219. Found: C, 71·60; H, 7·78; N, 6·36; mol. wt., 211 (cryoscopic method in benzene). Infrared bands: 1395, 1370 cm^{-1} (*tert.*-butyl group); no band in the 2250 cm^{-1} region.

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4:6-DINITROBENZOFUROXAN, NITROBENZODIFUROXAN AND BENZOTRIFUROXAN: A NEW SERIES OF COMPLEX-FORMING REAGENTS FOR AROMATIC HYDROCARBONS*

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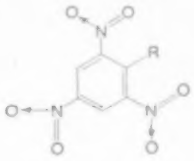
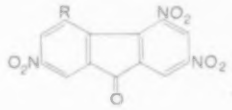
Abstract—4:6-Dinitrobenzofuroxan, 5:6-dinitrobenzofuroxan, nitrobenzodifuroxan and benzotrifuroxan have been prepared, and the values of the equilibrium constants for complex formation between naphthalene and this series of compounds have been determined in chloroform solution. Benzotrifuroxan has yielded solid complexes with a wide range of aromatic hydrocarbons.

THE formation of solid complexes between aromatic compounds containing electron-attracting groups (acceptors, *a*) and aromatic hydrocarbons (donors, *b*) is well known, and over seventy compounds that form solid complexes with naphthalene are listed.[2] The two most important acceptors in general use are 1:3:5-trinitrobenzene (I, R = H) and picric acid (I, R = OH). In 1946–47, 2:4:7-trinitrofluorenone (II, R = H) was introduced as a reagent forming complexes with a wide range of aromatic hydrocarbons, and it appears to be especially useful with polynuclear hydrocarbons.[3] More recently,[4] 2:4:5:7-tetranitrofluorenone (II, R = NO_2) has been used for this



(I)



(II)

purpose. Compounds such as (II) have high melting points and are rather insoluble in cold solvents; this is a disadvantage when dealing with aromatic hydrocarbons whose complex-forming power is small. For example, although 2-*n*-butylnaphthalene forms a solid complex with 1:3:5-trinitrobenzene,[5] it does not give a complex with 2:4:7-trinitrofluorenone.[6]

Of the mononuclear acceptors 1:3:5-trinitrobenzene appeared to be the most efficient complex-forming substance; for example, it forms solid complexes with 1- and 2-*n*-pentylnaphthalene, but picric acid does not yield solid complexes with these hydrocarbons.[5] Sinomiya[7] has concluded that maximum stability in complexes is obtained with acceptors in which the nitro groups are allowed to be coplanar with

* For preliminary communication, see Bailey and Case.[1]

[1] A. S. Bailey and J. R. Case, *Proc. Chem. Soc.* 176 (1957); erratum, *Ibid.* 211 (1957).
[2] *Encyclopaedia of Organic Chemistry* (Vol. 12B) p. 38. Elsevier, Amsterdam (1948).
[3] M. Orchin and E. O. Woolfolk, *J. Amer. Chem. Soc.* **68**, 1727 (1946); M. Orchin, L. Reggel and E. O. Woolfolk, *J. Amer. Chem. Soc.* **69**, 1225 (1947).
[4] M. S. Newman and W. B. Lutz, *J. Amer. Chem. Soc.* **78**, 2469 (1956).
[5] A. S. Bailey, G. B. Pickering and J. C. Smith, *J. Inst. Petrol.* **35**, 103 (1949).
[6] C. M. Staveley, D. Phil. Thesis, Oxford University (1955).
[7] T. Sinomiya, *Bull. Chem. Soc. Japan* **15**, 92, 137, 259, 281 (1940).

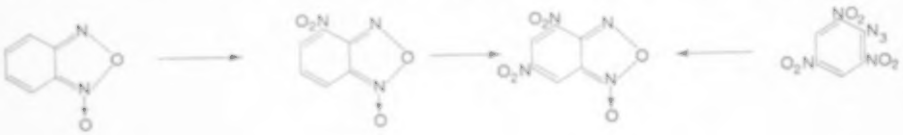
the benzene ring to which they are attached; association constants for the reaction between anthracene and a series of substituted 1:3:5-trinitrobenzenes in chloroform solution have been measured,[8] K decreasing in the order (I, R = H, OH, OMe, Cl, I). These results show that replacement of the hydrogen atoms in (I, R = H) by other groups leads to a decrease in complex-forming ability.

In 1899 Drost[9] reported that 4:6-dinitrobenzofuroxan (III) formed a solid complex with naphthalene. Examination of the structure of a benzofuroxan carrying a nitro group in the benzene ring in the "*ortho*" position to the furoxan ring shows that two identical structures might be written, and that resonance between the two canonical forms would give a planar hybrid structure. Hence this compound is similar to

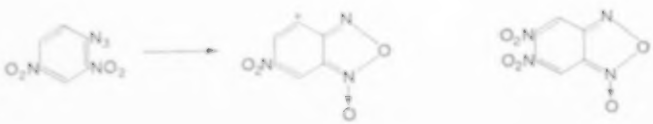
(III)

trinitrobenzene, but more highly substituted yet still planar. So one might expect (III) to be a more effective complex-forming reagent than (I, R = H). Drost's report of the formation of a naphthalene complex was confirmed and (III) also gave a complex with 1-*n*-pentylnaphthalene.[6] It was, therefore, decided to prepare a series of benzofuroxans containing nitro groups, to determine their association constants with a given hydrocarbon (naphthalene), and to try to obtain solid complexes, especially with hydrocarbons which do not yield complexes with (I) and (II).

Benzofuroxans are obtained (i) by decomposition of *o*-nitroazides and (ii) by oxidation of *o*-nitroanilines with either alkaline hypochlorite[10,11] or phenyl iodosoacetate.[12] Nitration of benzofuroxan (IV) yields 4-nitrobenzofuroxan (V),[9] and



(IV) (V) (III) (VI)



(VII) (VIII) (IX)

[6] S. D. Ross, M. Bassin and I. Kuntz, *J. Amer. Chem. Soc.* **76**, 4176 (1954).
[9] P. Drost, *Liebigs Ann.* **307**, 49 (1899).
[10] A. G. Green and F. M. Rowe, *J. Chem. Soc.* 2452 (1912).
[11] A. G. Green and F. M. Rowe, *J. Chem. Soc.* 2023 (1913).
[12] K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.* 4499 (1954).

4:6-dinitrobenzofuroxan (III);[9,11] this compound may also be obtained by decomposition of picryl azide (V).[13] Decomposition of 2:4-dinitrophenyl azide (VII) yields 5-nitrobenzofuroxan (VIII);[9] the azide may be obtained from 2:4-dinitroaniline[14] or by the reaction of 2:4-dinitrochlorobenzene with sodium azide.[15] Benzofuroxans have generally been obtained by heating the solid azide or by heating under reflux a benzene or toluene solution of the compound.[9,13,14] These methods often yield tarry material and the products require extensive purification. Of several solvents tried, glacial acetic acid appears to be the most suitable. Drost stated[9] that nitration of 5-nitrobenzofuroxan (VIII) with fuming acid gave 5:6-dinitrobenzofuroxan (IX) in unspecified yield. The substance was shown to be (IX) by reduction to 1:2:4:5-tetraaminobenzene (identified by colour reactions). (IX) gave a yellow naphthalene complex (m.p. and analysis not stated); unlike 4:6-dinitrobenzofuroxan (III), it did not give a colour with sodium hydroxide solution, and with aniline it gave a red compound, formed by the following reaction:

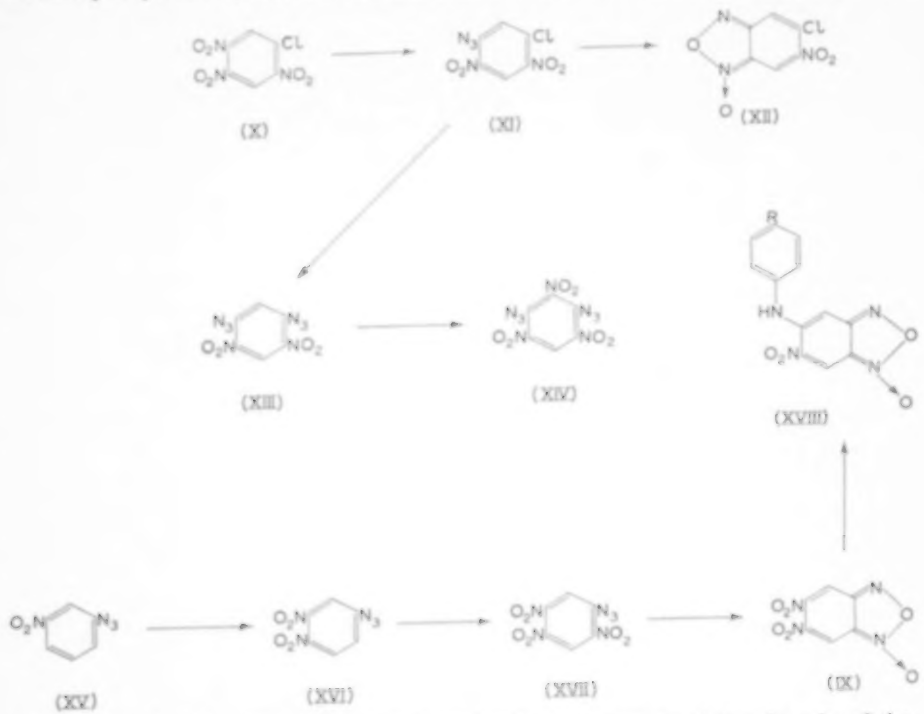
$$C_6H_2(NO_2)_2(NO)_2 + 2C_6H_5NH_2 = C_6(NO_2)_2(NO)_2(NHC_6H_5)_2 + 2H_2$$

Three features of 5:6-dinitrobenzofuroxan were of interest: (*i*) the m.p. (172°) is identical with the m.p. of (III), (*ii*) the compound should be less efficient as a complex-forming reagent than (III), and (*iii*) the attack on 5-nitrobenzofuroxan to give 5:6-dinitrobenzofuroxan (IX) is unexpected. Benzofuroxan itself is nitrated easily to give over 80 per cent of 4-nitrobenzofuroxan (V), a position "*ortho*" to the furoxan ring being attacked. One would therefore expect that further substitution in (VIII) would occur at the position marked (*), which is *meta* to the nitro group and *ortho* to the furoxan ring, to give 4:6-dinitrobenzofuroxan (III) and not 5:6-dinitrobenzofuroxan (IX). 5-Nitrobenzofuroxan was nitrated with fuming nitric acid as described by Drost. The crude product (50 per cent yield) had m.p. 130–150°, analysed for a dinitrobenzofuroxan and pure (III) was isolated in 30 per cent yield. 5:Nitrobenzofuroxan (VIII) was also nitrated under the conditions used in the nitration of (IV) to give (III) (an excess of concentrated sulphuric acid being used). A small quantity of crystals was obtained, m.p. 169–170°, which on analysis had values for a dinitrobenzofuroxan, but the infra-red and ultra-violet spectra of the compound were different from the spectra of (III).

The synthesis of 5:6-dinitrobenzofuroxan (IX) was next attempted from 2:4:5-trinitrochlorobenzene (X), the latter being obtained by nitration of *m*-chloronitrobenzene.[16] Holleman reports[17] the method as unsatisfactory. A single recrystallisation of the reaction product from trichloroethylene gives a 50 per cent yield of pure material. Treatment of 2:4:5-trinitrochlorobenzene (X) with one equivalent of sodium azide gave 1-azido-5-chloro-2:4-dinitrobenzene (XI), which, on being heated in acetic acid solution, yielded 5-chloro-6-nitrobenzofuroxan (XII). With two equivalents of sodium azide (X) gave 1:5-diazido-2:4-dinitrobenzene (XIII), m.p. 94–95° (dec.), which was further nitrated to form styphnyl azide (XIV); the formation of (XIV) proves the structure of (XIII). The nucleophilic displacement of the nitro group of

[13] E. Schrader, *Ber. Dtsch. Chem. Ges.* **50**, 777 (1917).
[14] R. J. Gaughran, J. P. Picard and J. V. R. Kaufman, *J. Amer. Chem. Soc.* **76**, 2233 (1954).
[15] F. Moulin, *Helv. Chim. Acta* **35**, 175 (1952).
[16] A. Laubenheimer, *Ber. Dtsch. Chem. Ges.* **9**, 760 (1876); R. Nietzki and W. Zänker, *Ber. Dtsch. Chem. Ges.* **36**, 3953 (1903).
[17] A. F. Holleman, *Versl. Gerwone Vergad. Akad. Amst.* **31**, 295 (1922); see also ref. 18.

(X) rather than the halogen atom is in agreement with the observation of Van de Vliet on the reactions of (X) with methoxide ion.[18] After we had successfully prepared nitrobenzodifuroxan and benzotrifuroxan by methods involving the nitration of an aromatic azide, we returned to the problem of synthesising (IX) by the nitration of *m*-nitrophenyl azide (XV). Nitration in cold fuming acid gave a solid analysing for a



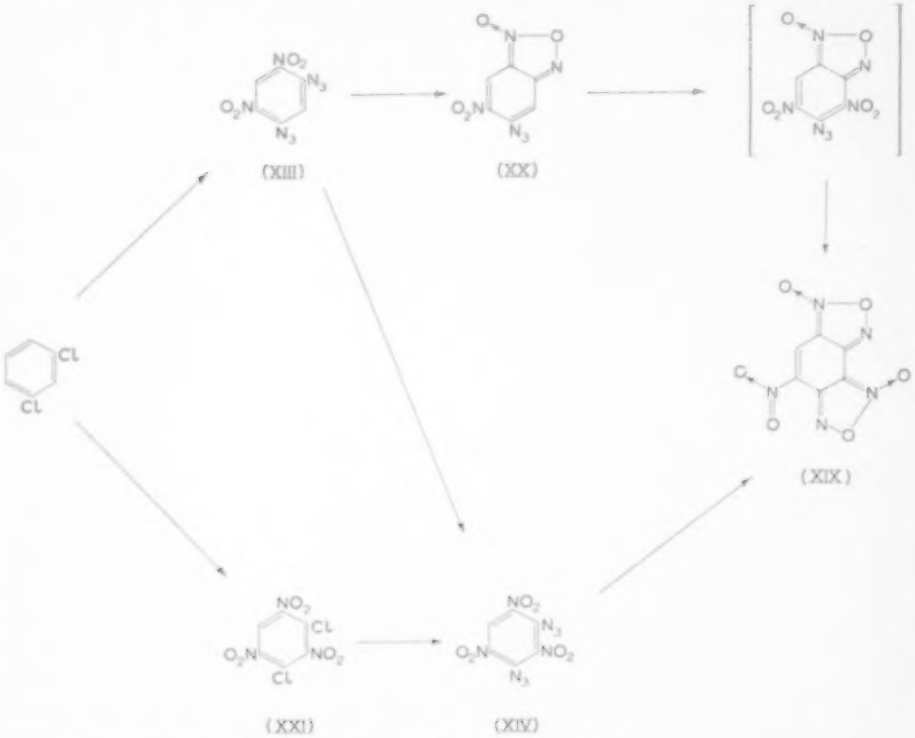
dinitrophenyl azide. The product was probably a mixture consisting largely of the 3:4-dinitro compound (XVI), since very little nitrogen was evolved on heating the compound at 100° in glacial acetic acid. Nitration with mixed acids gave a trinitrophenyl azide (m.p. 73–74°) consisting largely of the required 2:4:5-trinitrophenyl azide (XVII), the 6-position of (XVI) being attacked in preference to the 2-position. The crude trinitrophenyl azide was decomposed to give 5:6-dinitrobenzofuroxan (IX), pale-yellow prisms, m.p. 177°. The compound did not give any colour with sodium hydroxide solution, in agreement with Drost's observations. The ultra-violet spectrum of the compound was identical with that of the product (m.p. 169–170°) obtained in minute amount by nitration of (VIII) with mixed acid. The infra-red spectra of the two specimens were identical, the bands of the "synthetic" specimen being much sharper than those of the compound of m.p. 170°. Structure (IX) is also confirmed by the ultra-violet spectrum of the compound (see later).

Treatment of the synthetic material with aniline in ethanol gave dark-red needles; the analytical figures agree with those quoted by Drost, who suggested a formula $C_{18}H_{12}O_6N_6$, and are also in agreement with a formula $C_{12}H_8O_4N_4$, suggesting that aniline reacts with (IX) by displacement of a nitro group with the formation of

[18] P. G. Van de Vliet, *Rec. Trav. Chim. Pays-Bas* **43**, 606 (1924).

5-anilino-6-nitrobenzofuroxan (XVIII, R = H) by analogy with the formation of 5-anilino-2:4-dinitrotoluene from aniline and 2:4:5-trinitrotoluene.[19] The corresponding *p*-bromoanilino compound has been obtained, the two alternative formulae for the product being $C_{18}H_{10}O_6N_8Br_2$ or $C_{12}H_7O_4N_4Br$. The analytical figures are in excellent agreement with the latter formula (XVIII, R = Br). Displacement of one of the nitro groups of 5:6-dinitrobenzofuroxan (IX) by aniline is further evidence that the two nitro groups in (IX) are *ortho* to each other. These results suggest that Drost did obtain an impure specimen (m.p. 5° low) of 5:6-dinitrobenzofuroxan (IX) by nitration of (VIII), since our observations agree closely with his descriptions of the reactions of (IX).

Nitrobenzodifuroxan (nitrotetranitrosobenzene, XIX) has been prepared by the nitration of tetranitrosobenzene [20] and, more recently,[14] from 1:5-diazido-2:4-dinitrobenzene (XIII) via 5-azido-6-nitrobenzofuroxan (XX) and 5-azido-4:6-dinitrobenzofuroxan (not isolated). These two methods give poor yields and the compound has

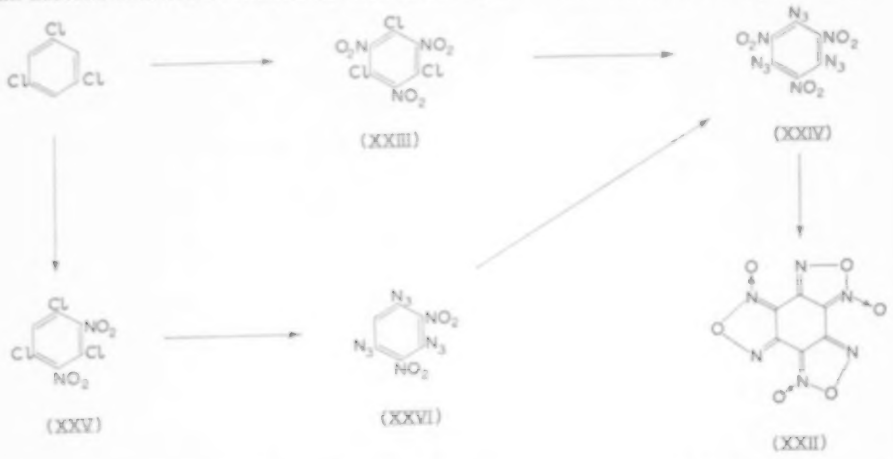


now been obtained from styphnyl chloride (XXI),[21,22] which, on treatment with sodium azide, gave an excellent yield of styphnyl azide (XIV), thermal decomposition of (XIV) yielding nitrobenzodifuroxan (XIX). 1:5-Diazido-2:4-dinitrobenzene (XIII) is easily obtained from 1:5-dichloro-2:4-dinitrobenzene and sodium azide;[14] (XIII) was smoothly nitrated to form styphnyl azide. The over-all yield of (XIX) from

[19] P. Hepp, *Liebigs Ann.* **215**, 366 (1882).
[20] R. Nietzki and W. Geese, *Ber. Dtsch. Chem. Ges.* **32**, 506 (1899).
[21] J. J. Sudborough and N. Picton, *J. Chem. Soc.* 591 (1906).
[22] A. T. Dann, *J. Chem. Soc.* 2461 (1929).

1:3-dichlorobenzene via styphnyl chloride (XXI) is 54 per cent; via (XIII) the yield is 55 per cent.

Benzotrifuroxan (hexanitrosobenzene, XXII) was described by Turek,[23] who obtained it from 1:3:5-trichlorobenzene via 1:3:5-trichloro-2:4:6-trinitrobenzene (XXIII) and 1:3:5-triazido-2:4:6-trinitrobenzene (XXIV). Although two nitro groups may easily be introduced into trichlorobenzene to form (XXV), the preparation of (XXIII) requires extremely vigorous conditions. When the method described by Turek was attempted, the mixture exploded, in agreement with the observations of Backer and Van der Baan,[24] and (XXIII) was obtained by a preparation involving the use of 60 per cent oleum.[25] We were unable to prepare triazidotrinitrobenzene (XXIV) by Turek's method; the transformation of (XXIII) into (XXIV) by shaking an acetone solution of the halide with moist sodium azide has been briefly reported.[26]



To avoid the preparation of (XXIII) the following route was devised. Reaction of the dinitro compound (XXV) with sodium azide affords 1:3:5-triazido-2:4-dinitrobenzene (XXVI).[27] The yield of (XXVI) is moderate, since it slowly decomposes at the temperature of its formation. Turek found that purification of (XXVI) was difficult, the m.p. of the substance being very sensitive to traces of impurity. We therefore nitrated the crude material, and triazidotrinitrobenzene (XXIV) crystallised from the nitrating mixture. The optimum reaction time for the step (XXV) → (XXVI) was determined by nitrating the crude reaction product and weighing the yield of pure (XXIV) produced. Turek decomposed the triazide in xylene; we first attempted its decomposition in acetic acid, but the compound only decomposed slowly in this solvent. Benzotrifuroxan was obtained by heating a solution of (XXIV) in propionic acid to 130–135°. The yields in all the stages of the preparation are good apart from the step (XXV) → (XXVI).

For the preparation of complexes we required a specimen of 2-phenylnaphthalene. This has been prepared[28] by a five-stage synthesis from benzyl cyanide and by heating

[23] O. Turek, *Chim. et Ind.* **26,** 785 (1931).
[24] H. J. Backer and S. Van der Baan, *Rec. Trav. Chim. Pays-Bas* **56,** 1178 (1937).
[25] P. Engelbertz, *Ger. Pat.* 767,510; *Chem. Abstr.* **49,** 14803d (1955).
[26] F. P. Bowden and H. T. Williams, *Proc. Roy. Soc.* A **208,** 176 (1951); A. Yoffé, *Ibid.* **208,** 188 (1951).
[27] O. Turek, *Chim. et Ind.* Special number 885 (June, 1933).
[28] N. Campbell and D. Kidd, *J. Chem. Soc.* 2154 (1954).

phenylethylene glycol with hydrobromic acid.[29] The glycol is converted into phenylacetaldehyde, which then undergoes self-condensation as soon as formed, and little polymeric material is produced. The hydrocarbon may also be obtained by heating phenylacetaldehyde at 170° with dilute hydrochloric acid.[30] By adding a solution of phenylacetaldehyde in acetic acid to boiling hydrobromic acid 2-phenylnaphthalene has been obtained in 52 per cent yield; this is a very simple method of obtaining small quantities of the hydrocarbon.

Spectral properties of the nitrobenzofuroxans and related compounds

The following ultra-violet spectra were measured in chloroform solution by means of a Cary recording spectrophotometer model 14M–50 (wavelengths in mμ.):

Benzofuroxan	λ_{max}	236	240	355	367		
	ε_{max}	1400	1700	7300	6500		
4-Nitrobenzo-	λ_{max}	234	267	407	412		
furoxan	ε_{max}	9700	3100	8300	8200		
5-Nitrobenzo	λ_{max}	240*		262	335	390	
furoxan	ε_{max}	8000		13,100	1800	5200	
4:6-Dinitrobenzo-	λ_{max}	234	260	277	330	412*	420
furoxan	ε_{max}	7950	12,500	13,400	1700	4900	7700
5:6-Dinitrobenzo-	λ_{max}	262	387				
furoxan	ε_{max}	17,150	5,050				
Nitrobenzo-	λ_{max}	238*		241	244	247*	
difuroxan	ε_{max}	10,600		11,150	11,000	10,200	
	λ_{max}	287*	291*	294	338	345*	356
	ε_{max}	7900	8200	8300	9800	9600	10,300
Benzotrifuroxan	λ_{max}	252*		258	280*		293*
	ε_{max}	23,600		27,900	10,000		7600

* Inflexion.

These spectra show several interesting features. 5-Nitrobenzofuroxan (VIII), 4:6-dinitrobenzofuroxan (III) and 5:6-dinitrobenzofuroxan (IX) all show strong absorption at 260–262 mμ, (IX) having the largest ε_{max}. This is probably associated with a nitro group not adjacent to the furoxan ring (nitrobenzene has λ_{max} 252 mμ, ε_{max} 10,000).[31] 4-Nitrobenzofuroxan (V) has a weak maximum at 267 mμ (see Fig. 1.) Introduction of a nitro group into the benzofuroxan nucleus alters the position of the longest wavelength band, (VIII) and (IX) both having maxima at 387–390 mμ. When a nitro group is *ortho* to the furoxan ring, the bathochromic effect is greater, (III) and (V) having λ_{max} 412–420 mμ. Thus the spectral properties of (IX) show that the two nitro groups are not *ortho* to the furoxan nucleus. Benzotrifuroxan has a strong band λ_{max} 255 mμ, ε_{max} 35,000 (in ethanol, slightly different from the values in chloroform). *cyclo*Hexenefuroxan has λ_{max} 262–263 mμ, ε_{max} 6700 (in ethanol).[32]

Infra-red spectra were determined in paraffin paste. Main bands above 1290 cm^{-1}

[29] H. E. Carter and E. J. Van Loon, *J. Amer. Chem. Soc.* **60**, 1077 (1938).
[30] K. Auwers and G. Keil, *Ber. Dtsch. Chem. Ges.* **36**, 3902 (1903).
[31] E. A. Braude, *Ann. Rep. Chem. Soc.* **42**, 126 (1945).
[32] J. H. Boyer, U. Toggweiler and G. A. Stoner, *J. Amer. Chem. Soc.* **79**, 1748 (1957).

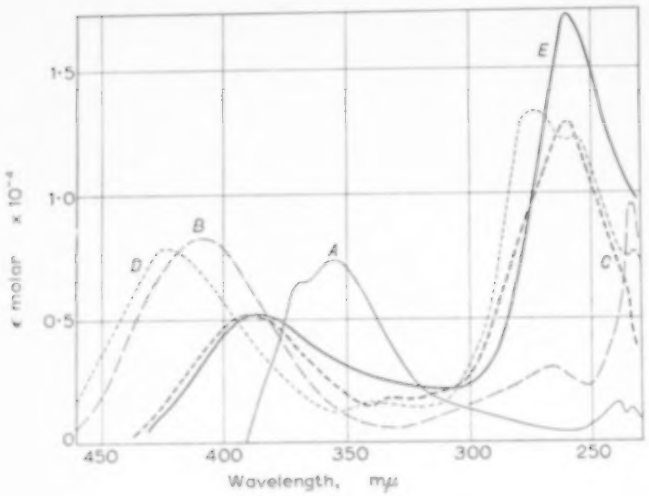


FIG. 1. Absorption spectra of:
A, benzofuroxan (———)
B, 4-nitrobenzofuroxan (— — —)
C, 5-nitrobenzofuroxan (- - - -)
D, 4:6-dinitrobenzofuroxan (. . . . .)
E, 5:6-dinitrobenzofuroxan (———)

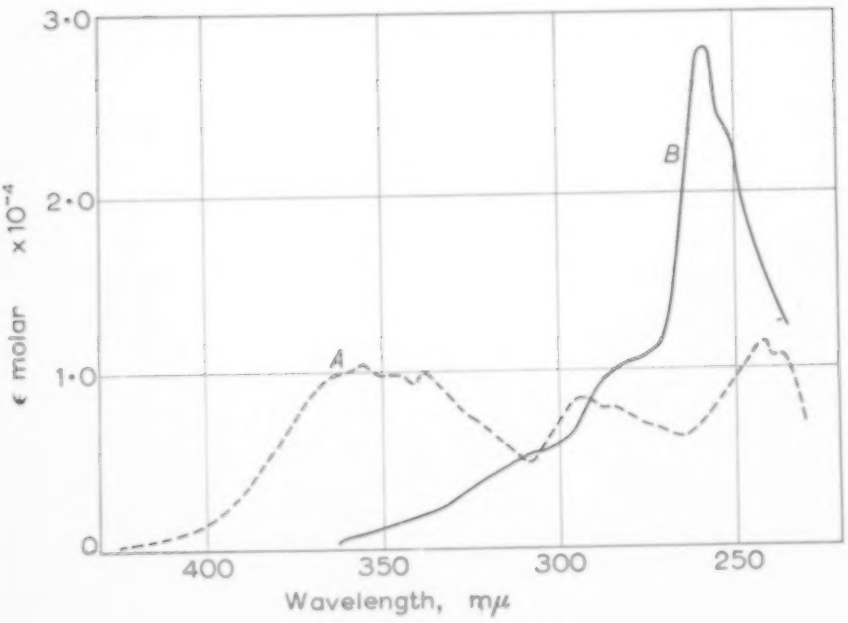


FIG. 2. Absorption spectra of:
A, nitrobenzodifuroxan (- - - -)
B, benzotrifuroxan (———)

are given, except for benzotrifuroxan for which the complete spectrum is quoted:

4-Nitrobenzofuroxan	3077;	1629;	1592;	1529;	1490;
	1439;	1359;	1326 cm^{-1}		
5-Nitrobenzofuroxan	3077;	1795;	1608;	1533;	1520;
	1484;	1403;	1351;	cm^{-1}	
4:6-Dinitrobenzofuroxan	3077;	1605;	1595;	1570;	1543;
	1456;	1344;	1328 cm^{-1}		
5:6-Dinitrobenzofuroxan	3077;	1766;	1626;	1608;	1563;
	1548;	1531;	1348;	1312 cm^{-1}	
Nitrobenzodifuroxan	3077;	1828;	1656;	1623;	1597;
	1563;	1529;	1522;	1429;	1342;
	1325;	1309;	1295 cm^{-1}		
Benzotrifuroxan	1656;	1608;	1572;	1540;	1508;
	1416;	1304;	1287;	1105;	1075;
	962;	935;	807;	735 cm^{-1}	

The N=O stretching vibration for monomeric nitrosobenzene is reported[33] as 1520 cm^{-1}; the absence of this band in the spectrum of (XXII) suggests it is not a simple nitroso compound. Boyer *et al.*[34] assigns the band at 1625–1600 cm^{-1} in the spectrum of simple benzofuroxans to the stretching vibration of $C{=}\overset{+}{N}{-}$. The intense band at 1656 cm^{-1} in the spectrum of (XXII) probably corresponds to this vibration.

Determination of spectrophotometric association constants

The equilibrium constants for complex formation between this series of compounds and naphthalene in chloroform solution have been determined

$$a + \text{naphthalene} \rightleftharpoons a \,.\, \text{naphthalene}$$

spectrophotometrically by the method of Foster *et al.*[35] Two master solutions were prepared, one containing the acceptor (*a*), the other containing pure naphthalene (*b*), and from them solutions containing a fixed amount of the acceptor and varying amounts of naphthalene were made up in calibrated flasks, the naphthalene being in large excess. One solution was prepared containing only (*a*) at the fixed concentration. This solution was placed in one of a pair of matching 1 cm cells fitted with lids and used as a blank instead of pure solvent. The optical densities of the solutions were measured in a Unicam SP 500 spectrophotometer. By using the solution containing only (*a*) in the "solvent" cell, the increase in optical density, ΔD, of the solution of $a + b$ was obtained directly from the spectrophotometer reading.[36]

For a 1:1 complex the equation relating ΔD, b and K is: $\Delta D/b = \text{constant} - K\Delta D$. Hence a plot of $\Delta D/b$ against ΔD should be a straight line of slope $-K$. The equation of the line of closest fit was obtained using the method of "least squares,"

[33] P. Tarte, *Bull. Soc. Chim. Belg.* **63**, 525 (1954).
[34] N. E. Boyer, G. M. Czerniak, H. S. Gutowsky and H. R. Snyder, *J. Amer. Chem. Soc.* **77**, 4238 (1955).
[35] R. Foster, D. Ll. Hammick and A. A. Wardley, *J. Chem. Soc.* 3817 (1953); see also R. Foster, D. Ll. Hammick and P. J. Placito, *J. Chem. Soc.* 3881 (1956); K. H. Takemura, M. D. Cameron and M. S. Newman, *J. Amer. Chem. Soc.* **75**, 3280 (1953); S. D. Ross and M. M. Labes *J. Amer. Chem. Soc.* **77**, 4916 (1955); *Ibid.* **79**, 76 (1957).
[36] W. Slough and A. R. Ubbelohde, *J. Chem. Soc.* 914 (1957); J. W. Watts, Part II Thesis, Oxford University (1956).

thus giving K. The equilibrium constant was determined at two wavelengths for each compound.

Purification of materials

Chloroform was washed with water six times, dried over calcium chloride, distilled and stored in the dark. A good specimen of *naphthalene* was crystallised from ethanol four times and the same batch was used for all our experiments; it had m.p. 80°. 1:3:5-*Trinitrobenzene* was crystallised from ethanol, m.p. 122°. 2:4:7-*Trinitrofluorenone* (obtained from Messrs. Hopkin & Williams Ltd.) was crystallised from acetic acid and it had m.p. 176·5°. The preparation and purification of other acceptors has been described elsewhere in this paper.

Ross and Labes reported a value of 1·30 at 24·8° for the equilibrium constant of the reaction between naphthalene and 1:3:5-trinitrobenzene in chloroform solution.[35]

TABLE 1. DETERMINATION OF THE EQUILIBRIUM CONSTANT FOR REACTION BETWEEN 2:4:7-TRINITROFLUORENONE AND NAPHTHALENE (b) IN CHLOROFORM SOLUTION

Concentration of trinitrofluorenone (a) = $4{\cdot}85 \times 10^{-4}$M
Wavelengths used 450 and 460 mμ. Temperature = 18°

	450 mμ		460 mμ	
(b) M	ΔD	$\frac{\Delta D}{b}$	ΔD	$\frac{\Delta D}{b}$
0·312	0·144	0·461	0·117	0·375
0·390	0·170	0·449	0·140	0·359
0·468	0·197	0·421	0·166	0·355
0·546	0·222	0·407	0·186	0·340
0·702	0·265	0·377	0·220	0·313
0·858	0·302	0·352	0·249	0·290

The lines of closest fit are:
$\Delta D/b = -0{\cdot}72\,\Delta D + 0{\cdot}590$ at 450mμ
$\Delta D/b = -0{\cdot}67\,\Delta D + 0{\cdot}444$ at 460 mμ
Mean value of K = 0·69 (l./mole)

TABLE 2. RESULTS FOR ASSOCIATION CONSTANTS IN CHLOROFORM SOLUTION

Acceptor	Temp (°C)	K [wavelength used (mμ)]	K [wavelength used (mμ)]	Mean value of K (l./mole)
2:4:7-Trinitrofluorenone	18	0·72 (450)	0·67 (460)	0·69
5:6-Dinitrobenzofuroxan	18	1·21 (440)	1·24 (450)	1·2
1:3:5-Trinitrobenzene	16	1·31 (410)	1·27 (420)	1·3
4:6-Dinitrobenzofuroxan	16	2·64 (478)	2·61 (482)	2·6
Nitrobenzodifuroxan	16	3·65 (470)	3·71 (480)	3·7
Benzotrifuroxan	19	4·13 (365)	4·09 (370)	4·1

These figures show clearly that complex-forming power increases steadily from 1:3:5-trinitrobenzene to benzotrifuroxan and that the position of the nitro group in the benzofuroxan nucleus is important, the value of K for 4:6-dinitrobenzofuroxan being twice the value of K for 5:6-dinitrobenzofuroxan.

Complexes with aromatic hydrocarbons

The formation of solid complexes between this series of compounds and other aromatic hydrocarbons was next investigated. In all the examples examined the solvent has been an acetic acid–ethanol mixture (1:4). Dimroth[37] has discussed the effect of the solubility of the various components on the formation of a solid complex, and this solvent mixture may not be the most suitable for all the pairs of compounds tried. To obtain some idea of the complex-forming ability of these compounds the formation of complexes with naphthalene (*A*), 2-phenylnaphthalene (*B*), 1-*n*-hexylnaphthalene (*C*), 1-phenylnaphthalene (*D*) (a hydrocarbon that is non-planar)[38] and tetrahydronaphthalene (*E*) was examined; the results are summarised in Table 3.

TABLE 3. COMPARISON OF COMPLEX-FORMING ABILITY

Acceptor	*A*	*B*	*C*	*D*	*E*
(IX)	+				
(III)	+	+	+		
(XIX)	+	+	(+)	+	+
(XXII)	+	+	+	+	+

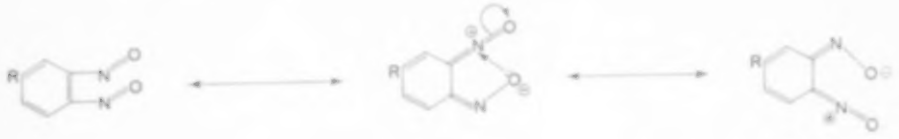
(IX). (*A*) was unstable at room temperature, whilst the isomeric (III). (*A*) was quite stable. (XIX). (*C*) was a sticky solid, which was not obtained pure or analysed. (XIX). (*E*) was a complex $C_{10}H_{12}\cdot 3C_6HO_6N_5$, whilst (XXII). (*E*) separated as a 1:1 complex. The scope of complex-formation was then extended more fully for benzotrifuroxan (XXII) for the following reasons. It alone formed sharp-melting complexes with (*D*) and (*E*); the 1:1 complex (XXII). (*A*) was the most stable in solution (as shown by the value of the association constant, K); and (XXII) was more soluble in the solvent used than (XIX). Twenty-four complexes have been prepared with benzotrifuroxan, of which the following are of interest, since the hydrocarbons do not form complexes readily with other reagents: 1:2:3-trimethylbenzene, mesitylene, 1:2:3:4-tetramethylbenzene, styrene, diphenyl, diphenylmethane, tetrahydronaphthalene, 6-methyltetrahydronaphthalene, 5-ethyltetrahydronaphthalene 5:7-dimethyltetrahydronaphthalene, 1:7-dimethyl-3:4-dihydronaphthalene, 2-α-naphthylbutane, 1-*n*-hexylnaphthalene, 2-*n*-octylnaphthalene, 1-phenylnaphthalene and indene. The complexes obtained from hydrocarbons such as alkylbenzenes, alkylnaphthalenes and tetrahydronaphthalenes gave clear melts (unless the m.p. was considerably over 200°); the complexes from "unsaturated" hydrocarbons such as styrene, indene and 1:7-dimethyl-3:4-dihydronaphthalene blackened and decomposed at the m.p.

[37] O. Dimroth and C. Bamberger, *Liebigs Ann.* **438**, 67 (1924); G. W. Wheland, *Advanced Organic Chemistry* p. 63. Wiley, New York (1949).

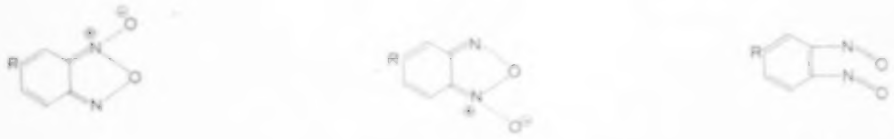
[38] R. A. Friedel, M. Orchin and L. Reggel, *J. Amer. Chem. Soc.* **70**, 199 (1948); M. Orchin and R. A. Friedel, *Ibid.* **71**, 3002 (1949).

The three xylenes, 2:3-di-*n*-hexylnaphthalene and 1:2:3:4:5:6:7:8-octahydroanthracene gave solids that on being analysed did not give values for a simple hydrocarbon to acceptor ratio; *p*-cymene, phenylacetylene, 1-phenyldialin, 6-ethyl tetrahydronaphthalene, 6-*n*-butyltetrahydronaphthalene and *cyclo*octatetraene all failed to give solid complexes. Although indole yielded a complex, no solid was obtained from quinoline or *iso*quinoline. We were interested to find that dimethylfulvene gave a stable solid derivative with (XXII). Trinitrobenzene also gave a yellow solid with dimethylfulvene. After standing at room temperature for 3–4 hr, the yellow product became colourless and had the same m.p. as trinitrobenzene. We were, however, able to obtain analytical results that showed that a complex had been formed.

The structure (XXVII a, b, c) and the name ψ-*o*-dinitrosobenzene have been suggested recently for the benzofuroxans.[39] Structures of type (XXVII) are important, especially in explaining why a monosubstituted benzofuroxan exists in only one form whilst isomers of type (XXXI) and (XXXII) are known in simple furoxans.[40] Resonance stabilisation of the benzene ring will result in (XXVII a) contributing more to the final state of a benzofuroxan than (XXXIII) will contribute to the final state of a simple furoxan. As transition states which permit interconversion of the isomers, (XXVII a) and (XXX) are more favourable energetically than (XXXIII).



(XXVII a) (XXVII b) (XXVII c)



(XXVIII) (XXIX) (XXX)

(XXXI) (XXXII) (XXXIII)

[39] J. H. Boyer, R. F. Reinisch, M. J. Danzig, G. A. Stoner and F. Sahhar, *J. Amer. Chem. Soc.* **77**, 5688 (1955).

[40] J. Meisenheimer, H. Lange and W. Lamparter, *Liebigs Ann.* **444**, 94 (1925).

It is, however, difficult to explain the well known stability of the benzofuroxans towards oxidation in terms of formula (XXVII). We have observed that benzofuroxan is not oxidised by performic and peracetic acids, reagents that oxidise *o*-nitronitrosobenzene to *o*-dinitrobenzene.[41] The placing of a double-headed arrow between (XXVII b) and (XXVII c) implies resonance between two canonical forms. This is unlikely, since *both* the oxygen atoms are in different positions in (XXVII b) and (XXVII c), and it is generally accepted[42] that "resonating structures must correspond to very nearly the same positions of all the atomic nuclei." In structure (XXVII b) there will be strong attraction between the positively charged nitrogen atom and the negatively charged oxygen atom leading directly to (XXVIII), the benzofuroxan structure. The compounds are hybrid structures, the canonical forms being (XXVII a, XXVII b, XXVIII) for one structure and (XXVII c, XXIX, XXX) for the other. We have, therefore, retained the well established name benzofuroxan for this class of compound to which it is impossible to assign a single formula.

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EXPERIMENTAL

Benzofuroxan was prepared by hypochlorite oxidation of *o*-nitroaniline.[10,11] 4-Nitrobenzofuroxan (IV) formed orange needles from methanol, m.p. 142°; Drost[9] reports m.p. 143°. Dinitration[11] of benzofuroxan afforded 4:6-dinitrobenzofuroxan (III) as long, yellow needles from acetic acid, m.p. 172° (lit.[9] 172°)

2:4-*Dinitrophenyl azide* (VII). A solution of sodium azide (9·0 g) in a mixture of methanol (20 ml), water (20 ml) and acetone (10 ml) was added slowly to a solution of 2:4-dinitrochlorobenzene (28 g) in acetone (20 ml) and methanol (20 ml) with vigorous shaking. After an hour the solution was poured into cold water, and the solid was collected, washed and dried. Yield 28·0 g (96 per cent), m.p. 66–67° (Moulin[15] gives m.p. 67–68°). A solution of 2:4-dinitrophenyl azide (25·0 g) in glacial acetic acid (50 ml) was heated on a steam-bath until evolution of nitrogen ceased (approximately 30 min). Next day 5-nitrobenzofuroxan (VIII) was collected, washed and dried (18·0 g), m.p. 71°. The mother-liquors were poured into water to give a further 5 g, m.p. 70° (Gaughran *et al.*[14] report m.p. 72°).

Nitration of 5-nitrobenzofuroxan. (*a*) 5-Nitrobenzofuroxan (4·0 g) was dissolved in ice-cold fuming nitric acid (sp. gr. 1·51, 6 ml), and the solution was set aside at room temperature for 15 hr and then poured into ice–water. The solid was collected, washed with water and dried; yield 2·5 g (50 per cent), m.p. 130–150° (Found: C, 32·6; H, 0·67; N, 25·2. Calc. for $C_6H_2O_6N_4$: C, 31·9; H, 0·89; N, 24·8 per cent). The infra-red spectrum of this material was almost identical with the infra-red spectrum of pure 4:6-dinitrobenzofuroxan. A naphthalene complex was obtained by mixing equimolecular quantities of the crude nitration product and naphthalene in hot methanol, long bright-red needles, m.p. 145–155° (Found: C, 54·0; H, 3·1; N, 15·9. Calc. for $C_6H_2O_6N_4 \cdot C_{10}H_8$: C, 54·3; H, 3·3; N, 15·8 per cent). The infra-red spectra of this complex and of the complex from pure 4:6-dinitrobenzofuroxan were identical. A small amount of the complex was decomposed by warming with trichloroethylene. On cooling, long yellow needles of pure 4:6-dinitrobenzofuroxan separated, m.p. 172° (mixed m.p. and infra-red spectra). The crude nitration product (1·0 g) was crystallised from a small amount of concentrated nitric acid to give 4:6-dinitrobenzofuroxan (0·6 g), (mixed m.p. and infra-red spectra). (*b*) 5-Nitrobenzofuroxan (5·0 g)

[41] R. Kuhn and W. van Klaveren, *Ber. Dtsch. Chem. Ges.* **71**, 779 (1938).
[42] G. W. Wheland, *op. cit.* p. 415.

was dissolved, by warming, in concentrated sulphuric acid (25 ml) and the solution was cooled to 0°. To the stirred solution was added an ice-cold mixture of fuming nitric acid (7·5 ml) and concentrated sulphuric acid (15 ml) during 30 min, the temperature being kept below 10°. The solution was then kept at room temperature for 30 min, slowly warmed to 40°, kept at that temperature for 15 min, cooled and poured on to ice. The semi-liquid mass was collected and dissolved in the minimum of boiling ethanol, and the solution was left to crystallise. Brown crystals separated; these were collected, washed and dried (2·0 g, 30 per cent), m.p. 128–145°. This material was crystallised three times from ethanol, the m.p. at each stage being 135–155°, 155–164° and 169–170°; the final yield of product was 20 mg (Found: C, 32·4; H, 0·93; N, 24·4. Calc. for $C_6H_2O_6N_4$: C, 31·9; H, 0·89; N, 24·8 per cent).

2:4:5-*Trinitrochlorobenzene* (X). Crystallisation from trichloroethylene gave a product, m.p. 113–115·5° (Found: C, 29·5; H, 0·85; N, 17·0. Calc. for $C_6H_2O_6N_3Cl$: C, 29·1; H, 0·81; N, 17·0 per cent). Accepted value[15] of m.p. 116°.

1-*Azido*-5-*chloro*-2:4-*dinitrobenzene* (XI). 2:4:5-Trinitrochlorobenzene (1·2 g) was dissolved in a mixture of acetone (3 ml) and methanol (3 ml). To this solution was added sodium azide (0·35 g) in water (1 ml) and methanol (1 ml). After 1 hr at room temperature the mixture was poured into water, and the solid was collected, washed and dried (1·1 g, 90 per cent). The *azide* was recrystallised from chloroform, to give yellow prisms, m.p. 80° (dec.) (Found: C, 30·0; H, 0·76; N, 27·2. $C_6H_2O_4N_5Cl$ requires C, 29·6; H, 0·83; N, 28·4 per cent). The azide was decomposed by heating in glacial acetic acid at 100° for 30 min. 5-*Chloro*-6-*nitrobenzofuroxan* (XII) separated from benzene–ethanol as fine, yellow needles, m.p. 88–89° (Found: N, 19·3; Cl, 15·9. $C_6H_2O_4N_3Cl$ requires N, 19·5; Cl, 16·5 per cent). Treatment of 2:4:5-trinitrochlorobenzene exactly as described before, except that sodium azide (0·7 g, 2 equiv.) was used, gave a product (1·10 g, 89 per cent), which crystallised from chloroform as yellow prisms, m.p. 94–95° (dec.) (Found: C, 29·2; H, 0·90; N, 45·6. Calc. for $C_6H_2O_4N_8$: C, 28·8; H, 0·80; N, 44·8 per cent). The substance was shown to be 1:5-diazido-2:4-dinitrobenzene (XIII) by the following method. The compound (0·2 g) was dissolved in cold fuming nitric acid (sp. gr. 1·51, 2 ml), and the solution was left overnight and then poured into water. The solid was collected, washed and dried (0·18 g). Crystallisation from chloroform gave pale-yellow needles, m.p. 91° (dec.). The infra-red spectrum of the compound was identical with that of styphnyl azide.

3:4-*Dinitrophenyl azide* (XVI). *m*-Nitrophenyl azide[43] (0·50 g, m.p. 52–53°) was dissolved in fuming nitric acid (3 ml), and next day the solution was poured into water, and the solid was collected, washed and dried (0·6 g, m.p. 89–91°). Crystallisation from methanol gave 3:4-*dinitrophenyl azide*, m.p. 91–92° (slight dec.) (Found: C, 34·7; H, 1·3; N, 33·2. $C_6H_3O_4N_5$ requires C, 34·5; H, 1·4; N, 33·5 per cent). When a solution of the compound in acetic acid was heated to 100°, very little nitrogen was evolved; the solution was diluted with a small quantity of water and left to crystallise. Pure 3:4-dinitrophenyl azide formed pale-yellow needles, m.p. 100–101°. This heating would convert any 2:3-dinitrophenyl azide into 4-nitrobenzofuroxan (orange needles, m.p. 142°) and any 2:5-dinitrophenyl azide into 5-nitrobenzofuroxan (m.p. 72°).

5:6-*Dinitrobenzofuroxan* (IX). *m*-Nitrophenyl azide (3·0 g) was dissolved in fuming nitric acid (14 ml) and the solution was added slowly to a cold mixture of fuming

[43] E. Noelting and O. Michel, *Ber. Dtsch. Ges.* **26**, 87 (1893).

nitric acid (14 ml) and concentrated sulphuric acid (14 ml), the temperature being kept below 20°. The dark brown solution was left overnight, when it became much paler. It was then poured on to ice, and the sticky yellow mass that separated was collected, rubbed with glacial acetic acid (10 ml) so that it solidified, water (30 ml) was added, and the whole mass was vigorously shaken. The solid that separated was collected, washed and dried, m.p. 60–70° (3·2 g, 76 per cent). Crystallisation gave the *trinitrophenyl azide*, yellow prisms (from methanol), m.p. 73–74° (dec.) (Found: C, 28·6; H, 0·57; N, 32·9. $C_6H_2O_6N_6$ requires C, 28·4; H, 0·79; N, 33·1 per cent). A solution of 2:4:5-trinitrophenyl azide (3·2 g) in acetic acid (10 ml) was heated on a water bath until evolution of nitrogen ceased (2 hr). The solution was cooled, water was added, and the solid was collected, washed and dried (2·3 g, m.p. 160–170°). The compound was crystallised from concentrated nitric acid to form hexagonal yellow prisms (1·4 g), m.p. 177° (without dec.), unchanged by further crystallisation (Found: C, 32·0; H, 1·2; N, 24·6. Calc. for $C_6H_2O_6N_4$: C, 31·9; H, 0·89; N, 24·8 per cent). Drost[9] reports m.p. 172° (dec.). Unlike (III), (IX) did not give a deep-red coloration when added to cold 2 N sodium hydroxide solution.

5-Anilino-6-nitrobenzofuroxan (XVII, R = H) was obtained by dissolving 5:6-dinitrobenzofuroxan in hot ethanol and adding 1 mol. of aniline. Clusters of dark-red needles separated, m.p. 168° (lit.[9] 168°) (Found: C, 53·4; H, 2·9; N, 20·3. $C_{12}H_8O_4N_4$ requires C, 52·9; H, 2·9; N, 20·6 per cent).

P-5-Bromoanilino-6-nitrobenzofuroxan (XVII, R = Br) formed dark-red needles, m.p. 151° (Found: C, 41·3; H, 2·1; N, 15·8; Br, 23·1. $C_{12}H_7O_4N_4Br$ requires C, 41·1; H, 2·0; N, 16·0; Br, 22·8 per cent).

1:5-*Dichloro*-2:4-*dinitrobenzene*. *m*-Dichlorobenzene (16·0 g) was dissolved in fuming nitric acid (40 ml), and the solution was heated on a steam bath for 1 hr, cooled and poured on to ice and the solid was collected (24 g). Crystallisation from ethanol gave a product (18 g), m.p. 101°. (lit.[21,22] m.p. 101°). This is more convenient than using a sulphuric–nitric acid mixture,[22] which requires vigorous stirring of the two phases.

Styphnyl azide (XIV). Styphnyl chloride was prepared as described by Sudborough and Picton.[21] A solution of sodium azide (13 g) in water (20 ml) and methanol (20 ml) was added slowly with stirring to a solution of styphnyl chloride (24 g) in acetone (20 ml) and methanol (20 ml). After 1 hr at room temperature the solution was poured into water, and the solid was collected, washed and dried (24·2 g), m.p. 85–87°. Crystallisation from methanol gave *styphnyl azide* as pale-yellow plates (21·2 g), m.p. 91–92° (dec.) (Found: C, 24·2; H, 0·68; N, 43·0. $C_6HO_6N_9$ requires C, 24·4; H, 0·34; N, 42·7 per cent).

Nitrobenzodifuroxan (XIX). A solution of styphnyl azide (2·5 g) in acetic acid (10 ml) was heated on a steam-bath until evolution of nitrogen ceased (2 hr). The solution was cooled, water (30 ml) was added, and the solid was collected (2·0 g, m.p. 154–156°). Crystallisation from chloroform–methanol (1:2) gave pale-yellow needles (1·7 g, 85 per cent), m.p. 158° (lit.[14] 156°) (Found: C, 30·4; H, 0·5; N, 29·1. Calc. for $C_6HO_6N_5$: C, 30·1; H, 0·4; N, 29·1 per cent).

1:5-Diazido-2:4-dinitrobenzene (XIII) was prepared from 1:5-dichloro-2:4-dinitrobenzene.[12] The compound crystallised as yellow plates from ethanol, m.p. 96–97° (dec.) (lit.[14] 78°) (Found: C, 29·0; H, 1·2; N, 45·9. Calc for $C_6H_2O_4N_8$: C, 28·8; H, 0·8; N, 44·8 per cent). Heating a solution of this azide in glacial acetic

acid for 30 min gave 5-azido-6-nitrobenzofuroxan (XX), as hexagonal plates from chloroform, m.p. 90° (lit.[12] 89°) (Found: C, 32·7; H, 0·85; N, 37·4. Calc. for $C_6H_2O_4N_6$: C, 32·4; H, 0·90; N, 37·8 per cent). The preparation of styphnyl azide by the nitration of (XIII) has been described earlier.

1:3:5-*Triazido*-2:4:6-*trinitrobenzene* (XXIV). Trichloroaniline[44] was deaminated[23] to form 1:3:5-trichlorobenzene, which was nitrated to give trichlorotrinitrobenzene.[25] Treatment of the last-named compound with sodium azide as described by Turek[23] gave an orange solid, m.p. 55–60°, which was not examined further. 1:3:5-Trichlorobenzene was nitrated[45] to give 1:3:5-trichloro-2:4-dinitrobenzene (XXV), m.p. 129–130°. (lit[45] 129–130°). 1:3:5-Trichloro-2:4-dinitrobenzene (10 g) was dissolved in a boiling mixture of acetone (55 ml) and methanol (20 ml) and a hot solution of sodium azide (8·2 g) in water (30 ml) and methanol (30 ml) was added. This mixture was boiled under reflux for 55 min and then filtered, and the residue of sodium chloride was washed with boiling ethanol (5–10 ml) and the filtrate and washings were cooled to 0° overnight. The crude triazidodinitrobenzene (XXVI) was collected and air-dried (6–7 g), m.p. 106–108°. Turek reported[27] that the product had m.p. 107–108° and that protracted crystallisation gave a solid of m.p. 116–117°. The crude material was slowly added to fuming nitric acid (5 ml per g of azide). When all the material was in solution, concentrated sulphuric acid (1 ml per g of azide) was added dropwise and the mixture was set aside at room temperature. After approximately 1 hr pale-yellow plates started to separate and 4 hr later the mixture was cooled to 0°. Next day the solid was collected and washed with water, m.p. 128–130°. The filtrate was diluted with an equal volume of water, and the impure material that separated was crystallised from acetic acid (total yield 4–5 g). The compound formed pale-yellow plates from acetic acid, m.p. 130–131° (lit.[23,26] 130–131°) (Found: C, 21·5; H, 0·19; N, 51·7, 48·3. Calc. for $C_6O_6N_{12}$: C, 21·4; H, 0·0; N, 50·0 per cent). The crystals were observed to darken on the surface. Decomposition of this azide was investigated in xylene, *iso*amyl acetate and propionic acid.

Benzotrifuroxan (XXII). Triazidotrinitrobenzene (3·0 g) was added to propionic acid (15 ml) and the mixture was kept in an oil-bath at 110-115° until all the solid had dissolved. The temperature of the bath was raised rapidly to 135° and maintained at that temperature for 5 min, and the temperature was then raised to 145° for a further 5 min. The pale-brown solution had then almost ceased to evolve nitrogen. It was filtered if necessary, cooled to ca. 60°, warm water (30 ml) was added, and the mixture was cooled to 0°. Next day the cream-coloured solid was collected (2·3 g, 86 per cent), m.p. 192–194°. Crystallisation from aqueous acetic acid or ethanol–acetic acid gave almost colourless prisms, m.p. 194–195° (slight dec.) (Found: C, 28·9; H, 0·08; N, 32·8. Calc. for $C_6O_6N_6$: C, 28·6; H, 0·0; N, 33·3 per cent). Turek[23] reports m.p. 195° (misquoted by Yoffé[26] as 159°). Crystallisation from ethanol gives crystals that turn slightly pink on the surface. The substance sublimes unchanged at 170°/15 mm. Crystallisation from benzene yields a *1:1 complex*, which loses benzene at 100° *in vacuo* (Found: C, 42·5; H, 1·8. $C_6H_6{\cdot}C_6O_6N_6$ requires C, 43·6; H, 1·8 per cent. Loss at 100°, 23·4, 23·8. Required loss, 23·6 per cent. Found on residue, C, 29·2 per cent). The residue from heating this complex is almost pure-white benzotrifuroxan. Instead of adding water to the propionic acid solution of (XXII),

[44] F. D. Chattaway and H. Irving, *J. Chem. Soc.* 142 (1933).
[45] E. J. E. Hüffer, *Rec. Trav. Chim. Pays-Bas* **40**, 451 (1921).

benzene (twice the volume of acid) may be added to precipitate benzotrifuroxan as its benzene complex. For reasons of safety we have never decomposed more than 5 g of this azide at once, although the reaction has never shown any sign of getting out of control.

2-*Phenylnaphthalene*. A solution of phenylacetaldehyde (10 g) in acetic acid (40 ml) was added dropwise to boiling hydrobromic acid (48%, 100 ml) during 40 min, and the mixture was then heated under reflux for a further 25 min and allowed to cool. The oily layer solidified. It was washed with water twice by decantation and crystallised from acetic acid (30 ml), to yield a solid (5·0 g), m.p. 98–101°. This was dissolved in benzene–light petroleum (boiling range 60–80°) mixture (1:2), the solution was passed through a short alumina column, the solvents were evaporated, and the residue was crystallised from methanol–ethanol to give 2-phenylnaphthalene (4·1 g), m.p. 102–103°. Evaporation of the mother-liquors yielded a further 0·3 g, m.p. 101–102° (lit.[28] 101–102°).

Preparation of complexes with aromatic hydrocarbons

The solvent used was a mixture of acetic acid and ethanol (1:4). Usually a slight excess (10 per cent) of the more soluble component (the hydrocarbon) was taken, the majority of the hydrocarbons forming 1:1 complexes. The solids that formed were collected, washed with a little methanol and dried at room temperature.

5:6-*Dinitrobenzofuroxan–naphthalene complex*. This formed orange needles, m.p. 115–150° (Found: C, 54·1; H, 2·6; N, 16·0. $C_{16}H_{10}O_6N_4$ requires C, 54·2; H, 2·9; N, 15·8 per cent). The compound decomposed on being kept at room temperature.

4:6-*Dinitrobenzofuroxan complexes*

Naphthalene, dark-red needles, m.p. 172° (dec.) in agreement with Drost.[9]

1-*n-Pentylnaphthalene*, soft red needles, m.p. 67·5–68·5° (Found: C, 59·4; H, 4·8; N, 12·9. $C_{21}H_{20}O_6N_4$ requires C, 59·4; H, 4·7; N, 13·2 per cent).*

1-*n-Hexylnaphthalene*, scarlet needles, m.p. 146–150° (Found: C, 60·1; H, 5·0; N, 12·6. $C_{22}H_{22}O_6N_4$ requires C, 60·5; H, 4·6; N, 12·8 per cent).

2-*Phenylnaphthalene*, shiny red plates, m.p. 130° (Found: C, 61·2; H, 3·0; N, 16·5. $C_{22}H_{14}O_6N_4$ requires C, 61·4; H, 3·3; N, 16·3 per cent).

Nitrobenzodifuroxan complexes

Naphthalene, orange needles, m.p. 183° (dec.) (Found: C, 52·3; H, 2·6; N, 18·6. $C_{16}H_9O_6N_5$ requires C, 52·3; H, 2·5; N, 19·1 per cent).

1-*Phenylnaphthalene*, dark-red needles, m.p. 97·5–98° (Found: C, 59·6; H, 2·9; N, 15·5. $C_{22}H_{13}O_6N_5$ requires C, 59·6; H, 2·9; N, 15·8 per cent).

2-*Phenylnaphthalene*, red plates, m.p. 120–121° (Found: C, 59·3; H, 3·2; N, 15·2 per cent).

Tetrahydronaphthalene, pale-yellow needles, softened at 140°, m.p. 145–148° (Found: C, 39·3; H, 1·9; N, 23·9. $C_{10}H_{12}{\cdot}3C_6HO_6N_5$ requires C, 39·6; H, 1·8; N, 24·3 per cent).

Benzotrifuroxan complexes

A solution of benzotrifuroxan (0·25 g, 0·01 mole) in acetic acid–ethanol (2 ml) was filtered on to the hydrocarbon (solids were dissolved in a small amount of warm

* With C. M. Staveley.

solvent); usually a precipitate formed and the mixture was warmed to give a clear solution, which was then allowed to cool.

Benzene, colourless needles, which turned into prisms between 80–100°, m.p. 195° (m.p. of benzotrifuroxan) (Found: C, 32·5; H, 1·0; N, 31·1. $C_6H_6{\cdot}5C_6O_6N_6$ requires C, 32·3; H, 0·5; N, 31·4 per cent).

1:2:3-*Trimethylbenzene*, pale-cream needles, m.p. 170–172° (Found: C, 48·2; H, 3·2; N, 22·5. $C_{15}H_{12}O_6N_6$ requires C, 48·4; H, 3·3; N, 22·6 per cent).

1:3:5-*Trimethylbenzene*, colourless plates, m.p. 162–165° (Found: C, 48·3; H, 3·2; N, 22·7 per cent).

1:2:3:4-*Tetramethylbenzene*, lemon-yellow needles, m.p. 190–193° (Found: C, 49·6; H, 4·0; N, 21·8. $C_{16}H_{14}O_6N_6$ requires C, 49·7; H, 3·7; N, 21·8 per cent).

Hexamethylbenzene, pale-yellow needles, m.p. 207° (dec.) (Found: C, 52·3; H, 4·5; N, 19·9. $C_{18}H_{18}O_6N_6$ requires C, 52·2; H, 4·4; N, 20·3 per cent).

Styrene, pale-cream spears, m.p. 148–150° (dec.) (Found: C, 46·8; H, 2·2; N, 23·6. $C_{14}H_8O_6N_6$ requires C, 47·2; H, 2·3; N, 23·6 per cent).

Diphenyl, pale-yellow needles, m.p. 164–166° (Found: C, 53·7; H, 2·4; N, 20·3. $C_{18}H_{10}O_6N_6$ requires C, 53·2; H, 2·5; N, 20·7 per cent).

Diphenylmethane, white waxy prisms, m.p. 73–83° (Found: C, 64·4; H, 4·0; N, 14·7. $2C_{13}H_{12}{\cdot}C_6O_6N_6$ requires C, 65·3; H, 4·1; N, 14·7 per cent).

Tetrahydronaphthalene, cream-coloured irregular plates, m.p. 151–152° (Found: C, 49·8; H, 3·2; N, 21·7. $C_{16}H_{12}O_6N_6$ requires C, 50·0; H, 3·2; N, 21·9 per cent).

6-*Methyltetrahydronaphthalene*, colourless needles, m.p. 128–135° (Found: C, 50·9; H, 3·5; N, 21·1. $C_{17}H_{14}O_6N_6$ requires C, 51·3; H, 3·5; N, 21·1 per cent).

5-*Ethyltetrahydronaphthalene*, pale-yellow needles, m.p. 144–147° (Found: C, 52·8; H, 4·0; N, 20·2. $C_{18}H_{16}O_6N_6$ requires C, 52·5; H, 3·9; N, 20·4 per cent).

5:7-*Dimethyltetrahydronaphthalene*, cream-coloured irregular plates, m.p. 132–136°, clearing at 148° (Found: C, 52·3; H, 3·6; N, 20·9 per cent).

1:7-*Dimethyl*-3:4-*dihydronaphthalene*, long lemon-yellow needles, m.p. 128–130° (dec.) (Found: C, 52·6; H, 3·4; N, 20·7. $C_{18}H_{14}O_6N_6$ requires C, 52·7; H, 3·4; N, 20·5 per cent).

Naphthalene, the complex crystallised from acetic acid as pale greenish-yellow needles, m.p. 250–252° (dec.) (Found: C, 51·0; H, 2·4; N, 21·6. $C_{16}H_8O_6N_6$ requires C, 50·6; H, 2·1; N, 22·1 per cent).

1:7-*Dimethylnaphthalene*, long yellow prisms, m.p. 215° (dec.) (Found: C, 53·5; H, 2·8; N, 20·4. $C_{18}H_{12}O_6N_6$ requires C, 52·9; H, 3·0; N, 20·6 per cent).

1-*n*-*Pentylnaphthalene*, pale-yellow needles, m.p. 126° (Found: C, 56·5; H, 3·9; N, 18·5. $C_{21}H_{18}O_6N_6$ requires C, 56·0; H, 4·0; N, 18·7 per cent).

1-n-*Hexylnaphthalene*, pale-yellow needles, m.p. 118° (Found: C, 56·7; H, 4·3; N, 18·0. $C_{22}H_{20}O_6N_6$ requires C, 56·9; H, 4·3; N, 18·1 per cent).

2-n-*Octylnaphthalene*, pale-yellow needles, m.p. 115–118° (Found: C, 58·9; H, 4·9; N, 16·9. $C_{24}H_{24}O_6N_6$ requires C, 58·5; H, 4·9; N, 17·1 per cent).

2-α-*Naphthylbutane*, yellow plates, m.p. 107–117° (Found: C, 55·0; H, 3·6; N, 18·8. $C_{20}H_{16}O_6N_6$ requires C, 55·1; H, 3·7; N, 19·3 per cent).

1-*Phenylnaphthalene*, pale-green crystals, m.p. 162° (Found: C, 51·9; H, 2·0; N, 21·6. $2C_{16}H_{12}{\cdot}3C_6O_6N_6$ requires C, 51·6; H, 2·1; N, 21·7 per cent).

2-*Phenylnaphthalene*, bright-yellow needles, m.p. 158° (Found: C, 58·0; H, 2·7; N, 18·3. $C_{22}H_{12}O_6N_6$ requires C, 57·9; H, 2·6; N, 18·4 per cent).

Indene, long pale-yellow laths, m.p. 168–170° (dec.) (Found: C, 49·2; H, 2·2; N, 22·5. $C_{15}H_8O_6N_6$ requires C, 48·9; N, 2·2; N, 22·8 per cent).

Indole (prepared in ethanol), pale-yellow needles, m.p. 180° (Found: C, 45·6; H, 2·1; N, 26·1. $C_{14}H_7O_6N_7$ requires C, 45·5; H, 1·9; N, 26·1 per cent).

Dimethylfulvene (prepared in ethanol), irregular bright-yellow plates, decomposing violently at 140° (Found: C, 46·9; H, 2·6; N, 23·3. $C_{14}H_{10}O_6N_6$ requires C, 46·9; H, 2·8; N, 23·5 per cent).

The following did not give correct results on analysis.

o-*Xylene*, clusters of rectangular plates, m.p. 152–155° (Found: C, 46·0; H, 2·3; N, 24·1. $C_{14}H_{10}O_6N_6$ requires C, 46·9; H, 2·8; N, 23·5 per cent).

m-*Xylene*, cream-coloured rods slowly separated, softened at 140°, m.p. 165–175° (Found: C, 45·2; H, 2·6; N, 24·4 per cent).

p-*Xylene*, irregular plates, m.p. 160–170° (Found: C, 41·5, 48·5; H, 2·8, 2·5; N, 24·9 per cent).

2:3-*Di*-n-*hexylnaphthalene*, pale-yellow needles, m.p. 93–103° (Found: C, 62·8; H, 6·3; N, 14·4. $C_{38}H_{32}O_6N_6$ requires C, 61·3; H, 5·9; N, 15·3 per cent).

1:2:3:4:5:6:7:8-*Octahydroanthracene*, pale-yellow plates, m.p. 110–120° (Found: C, 63·6, 63·7; H, 5·3, 5·7; N, 15·4. $3C_{14}H_{18}{\cdot}2C_6O_6N_6$ requires C, 61·1; H, 5·1; N, 15·8 per cent).

1:3:5-*Trinitrobenzene–dimethylfulvene complex*

The *complex* separated from the ethanol solution of the components as yellow laths, m.p. 72–73° (Found: C, 46·5; H, 3·2; N, 15·2. $(C_6H_3N_3O_6)_9{\cdot}(C_8H_{10})_5$ requires C, 46·1; H, 3·2; N, 15·5 per cent). The compound became white in colour in 3–4 hr at room temperature (m.p. 120°; 1:3:5-trinitrobenzene, mixed m.p. 120°).

Acknowledgements—We thank Drs. B. R. Brown, M. C. Whiting, S. A. Miller and J. C. Smith for gifts of hydrocarbons.

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THE STRUCTURE OF LAGIDZE'S *CYCLO*BUTADIENE DERIVATIVES—I*

THE "$C_{14}H_{10}$ HYDROCARBON"

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Abstract—The hydrocarbon resulting from the reaction of benzene with the diacetate of but-2-yne-1,4-diol in presence of aluminum chloride is shown to be 2-phenylnaphthalene, and not a benz*cyclo*butadiene derivative, as has been suggested.

AMONG the hydrocarbons of theoretical interest to the organic chemist, the unknown *cyclo*butadiene (I) is perhaps the simplest. Experiments directed towards the synthesis of compounds containing a simple *cyclo*butadiene system have so far all failed,[1,2,3,4,5] although a dimer of tetramethyl*cyclo*butadiene has apparently been prepared.[6,7]

I

Our interest in this field was occasioned by a report of Lagidze and Petrov,[8] stating that a hydrocarbon, $C_{14}H_{10}$ (m.p. 102°), prepared by reaction† of benzene, aluminum chloride and the diacetate of but-2-yne-1,4-diol probably possessed the structure of a benz*cyclo*butadiene derivative (II). Much of the data appeared to be in

II

III

* Adapted from the B.A. thesis of Harry W. Taber, Reed College, May 1957.

† In the description of this synthesis (cf. Lagidze and Petrov[8]) mention is made of two other products, namely 4-acetoxy-1-chlorobut-2-yne (in an unstated yield), and an acetophenone derivative (20 per cent). We have been unable to duplicate the formation of these products, and also the yield (12 per cent) claimed for the 102° hydrocarbon (see under "Experimental").

[1] D. R. Howton and E. R. Buchman, *J. Amer. Chem. Soc.* **78**, 4011 (1956); D. E. Applequist and J. D. Roberts, *J. Amer. Chem. Soc.* 4012.
[2] A. T. Blomquist and J. A. Verdol, *J. Amer. Chem. Soc.* **77**, 806 (1955).
[3] E. F. Jenney and J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 2005 (1956); E. F. Silversmith and J. D. Roberts, *Ibid.* 4023.
[4] D. P. Craig, *J. Chem. Soc.* 3175 (1951); J. D. Roberts, A. Streitwieser and C. M. Regan, *J. Amer. Chem. Soc.* **74**, 4579 (1952).
[5] H. C. Longuet-Higgins and L. E. Orgel, *J. Chem. Soc.* 1969 (1956).
[6] I. V. Smirnov-Zamkov, N. A. Kostromina and G. A. Piskovitina, *Ukr. Khim. Zh.* **22**, 67 (1956): *Chem. Abstr.* **50**, 13761c (1956).
[7] R. Criegee and G. Louis, *Chem. Ber.* **90**, 417 (1957).
[8] R. M. Lagidze and A. D. Petrov, *Dokl. Akad. Nauk SSSR* **83**, 235 (1952); *Chem. Abstr.* **47**, 4321g (1953); *Chem. Zentr.* **125**, 1713 (1954): *Note added in proof*, 1 *March* 1958. LAGIDZE[8a] has recently published a retraction of his former views concerning the "$C_{14}H_{10}$ hydrocarbon" and his latest interpretations agree with those expressed here; cf. also a recent note by Maier.
[8a] R. M. Lagidze, *Soobshchenya Akad. Nauk Gruzin. SSR* **19**, 279 (1957).
[6a] G. Maier, *Chem. Ber.* **90**, 2949 (1957).

conflict with the reactions to be expected of a compound of this structure. Thus Lagidze and Petrov found that the hydrocarbon was stable to permanganate in the cold, that after ozonolysis it yielded formic and benzoic acids, and that on oxidation with chromic acid in acetic acid a yellow diketone, $C_{14}H_8O_2$, was formed.

It should be pointed out that, in their first paper, Lagidze and Petrov[8] assigned structure (III) to the $C_{14}H_{10}$ hydrocarbon, but, when it was found to be stable to permanganate, structure (II) was adopted. The possibility that the $C_{14}H_{10}$ hydrocarbon, m.p. 102°, was phenanthrene ($C_{14}H_{10}$, m.p. 101°) was abandoned, since a mixture of the two hydrocarbons showed a depression of the m.p. Compare also the monobromo substitution product of (II), m.p. 66°, and 9-bromophenanthrene, m.p. 63°.[9] It seemed possible also that the "yellow diketone" reported by Lagidze and Petrov[8] was a quinone (it gave a colored monoxime), but no compound corresponding to these properties derived from a $C_{14}H_{10}$ hydrocarbon has been reported in the literature.

Recent work by Cava and Napier[10] on the synthesis and properties of benz*cyclo*butadiene (IV) has also raised doubts as to the correctness of formulation of the 102°

IV V VI

hydrocarbon as (II). Thus although the saturated derivative (VI) proved stable, the compound (IV) appeared to dimerize readily via a Diels–Alder reaction to give (V) as the sole isolable material. It would therefore seem that the stability, if any, afforded to *cyclo*butadiene (I) by fusion with a benzene ring as in (IV) is not of practical significance as far as isolation of the compound is concerned. Thus were the "$C_{14}H_{10}$ hydrocarbon" to possess structure (II), Diels–Alder self-condensation would be expected, ending in polymerization.

Mention should also be made of a further related structure, namely that of diphenylene (VII).[11] This stable hydrocarbon bears only a passing formal resemblance to

VII

(I), since it would be expected that the apparent *cyclo*butadiene system present in structure (VII) would become incorporated into two essentially separate benzenoid systems.

In the light of the foregoing, the latest structure (VIII) favored by the Russian workers[12] for the 102° hydrocarbon is perhaps more reasonable than the previous ones, since no benz*cyclo*butadiene system is present. Nevertheless, this structure is not without its objections, since oxidation would presumably lead to *o*-phthalic acid, not benzoic acid, and also isomerization to anthracene would be expected: none was

[9] *Beilsteins Handbuch, Hauptwerk* **5**, 671.
[10] M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.* **78**, 500 (1956); *Ibid.* **79**, 1701, 1706 (1957).
[11] W. C. Lothrop, *J. Amer. Chem. Soc.* **63**, 1187 (1941).
[12] R. M. Lagidze, *Trud. Inst. Khim. Akad. Nauk Gruzin. SSR* **12**, 157 (1956); (in English translation by Associated Technical Services, P.O. Box 271, East Orange, New Jersey).

reported by the Russian workers (but see under "Experimental"). The conditions required for the synthesis of the 102° hydrocarbon—aluminum chloride at room temperature in benzene solution, followed by heating at 90° for 10 hr—would seem to facilitate aromatization of the above-mentioned kind.[13]

VIII

In view of these facts, it became necessary to re-investigate the structure of the "$C_{14}H_{10}$ hydrocarbon". The first four attempts yielded only viscous yellow oils, which did not crystallize in a refrigerator on standing. At this stage a written exchange with Professor Lagidze in Tbilisi assured us that the reaction was in fact feasible, and that he himself had recently checked the synthesis after we had informed him of our failures. At the second of three subsequent attempts we were successful in obtaining solid material, and the distilled reaction product solidified at once to a pale yellow mass of plates, which on crystallization from ethanol afforded colorless crystals, m.p. 102–103°. In agreement with the findings of the Russian workers, this substance gave a depression of m.p. when mixed with phenanthrene.

Evidently the conditions of the synthesis of the 102° hydrocarbon are quite critical: Lagidze himself informed us (in a personal communication, October 1956) that in some runs he had obtained viscous non-crystallizable oils, but he was unable to account for this erratic behavior.

The first indication that the molecular formula was not $C_{14}H_{10}$ resulted from the fact that the peak of highest *m/e* in the mass spectrum of the 102° hydrocarbon appeared at 204, suggesting $C_{16}H_{12}$ as a possible formula. The fact that the infrared spectrum of our 102° hydrocarbon matched that of 2-phenylnaphthalene provided the last clue to the identification of the substance. A sample prepared by the method of Elks and Hey[14] also melted at 102–103°, and showed no depression of m.p. on mixing. Further, the ultraviolet absorption of our hydrocarbon in methyl*cyclo*hexane showed λ_{max} at 249 and at 286 mμ. The published[15] spectrum in *cyclo*hexane also showed these maxima, as did a spectrum of the 102° hydrocarbon (in *n*-heptane) kindly furnished by Prof. Lagidze.

There can thus be no reasonable doubt that the 102° hydrocarbon is 2-phenylnaphthalene. The experimental data reported by the Russian workers can now be explained with reference to compounds most of which are already known (cf. Table 1).

Except for the molecular-weight data reported by Lagidze and Petrov, it is readily seen that the properties of the "$C_{14}H_{10}$ hydrocarbon" described by them correspond very closely with those of 2-phenylnaphthalene. Evidently too great an emphasis was placed by the Russian workers on combustion-analysis data (ambiguous in this case) and unfortunately the molecular-weight values they obtained were too low: the caus'

[13] M. Turova-Pollak and M. Lukina, *J. Gen. Chem. USSR* **18,** 179 (1948); H. Pines, W. D. Huntsman and V. N. Ipatieff, *J. Amer. Chem. Soc.* **75,** 2315 (1953).
[14] J. Elks and D. H. Hey, *J. Chem. Soc.* 441 (1943).
[15] R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds.* John Wiley, New York (1951); R. A. Friedel, M. Orchin and L. Reggel, *J. Amer. Chem. Soc.* **70,** 200 (1948); W. M. Kutz, J. E. Nickels, J. J. McGovern and B. B. Carson, *Ibid.* **70,** 4029 (1948)

of this remains obscure, since Chattaway and Lewis[16] many years ago successfully determined the molecular weight of 2-phenylnaphthalene by the same method as that used by Lagidze and Petrov, i.e. a cryoscopic measurement in benzene.

TABLE 1.—COMPARISON OF DATA CONCERNING THE "$C_{14}H_{10}$ HYDROCARBON" AND 2-PHENYLNAPHTHALENE

Nature of data	Results of Lagidze and Petrov	Required on the basis of "$C_{14}H_{10}$"	For 2-phenyl-naphthalene[17]
Analysis of hydrocarbon	Found: C, 94·34 94·10, 94·21; H, 5·78, 5·78, 5·77	C, 94·34 H, 5·66	C, 94·08 H, 5·92
Molecular weight of hydrocarbon	188 ± 10 (X-ray) 177–184 (cryoscopic)	178	198 (cryoscopic[16]). Found: 204 (mass-spectrometer[18])
Monobromo compound	m.p. 65°		m.p. 66°
Mononitro compound	m.p. 129°, yellow crystals. Found: N, 5·84	Calcd. for $C_{14}H_9O_2N$: N, 6·27	m.p. 127° yellow needles. Calcd. for $C_{16}H_{11}O_2N$: N, 5·62
Diketone	m.p. 111–112°, lemon-yellow crystals. Found: C, 81·87; H, 4·37	Calcd. for $C_{14}H_8O_2$: C, 80·80 H, 3·84	m.p. 109°, yellow needles. Calcd. for $C_{16}H_{10}O_2$: C, 81·8 H, 4·28
Monoxime	m.p. 176°, red crystals. Found: N, 5·79, 5·89	Calcd. for $C_{14}H_9O_2$(sic)*: N, 6·26	Calcd. for $C_{16}H_{11}O_2N$: N, 5·63

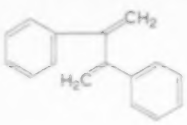
The mechanism of formation of 2-phenylnaphthalene (XI) from (IX) and (X) appears to involve a series of changes; it is evident that rearrangements must be involved (since direct substitution would yield dibenzylacetylene, $C_{16}H_{14}$), and also a

IX X XI

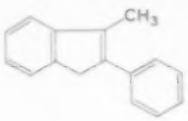
dehydrogenation, since 2-phenylnaphthalene has the molecular formula $C_{16}H_{12}$. Until further studies (which we hope to describe in future communications) are complete, we defer a complete discussion of the mechanism: we think it likely, however, that the intermediary formation of 2,3-diphenylbutadiene is involved; this is known[19] to

[16] F. D. Chattaway and W. H. Lewis, *J. Chem. Soc.* **65**, 873 (1894).
[17] D. H. Hey and S. E. Lawton, *J. Chem. Soc.* 374 (1940).
[18] Present work.
[19] W. Hausmann and A. E. Wilder Smith, *J. Chem. Soc.* 1030 (1949).

isomerize to (XIII) in presence of hydrogen chloride (produced during the synthesis

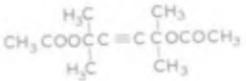


XII



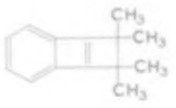
XIII

of the 102° hydrocarbon). Conversion of (XIII) to (XI) may be effected by dehydrogenation[20] and ring expansion in presence of aluminum chloride or some other similar Lewis acid. We were led by such mechanistic reasoning to the conclusion that the synthesis of a hydrocarbon from (XIV)—i.e. the tetramethyl analog of (X)—by

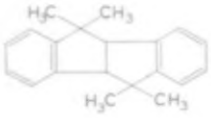


XIV

the procedure of Lagidze and Petrov should lead not to the structure (XV) as postulated by Lagidze and Loladze,[21] but most probably to the known hydrocarbon (XVI).[22] Very recently we have been successful in showing that this is so, and these studies will be described in Part II of this series.[23]



XV



XVI

EXPERIMENTAL

But-2-yne-1,4-diol diacetate (X)

Forty-eight grams of but-2-yne-1,4-diol* (recrystallized from ethyl acetate) was dissolved in 90 g of pyridine that had been dried over potassium hydroxide. Benzene (112 ml, reagent grade) was added as solvent, followed by 123 g of acetic anhydride in small portions, with agitation and cooling in ice (the temperature was maintained below 30°). When addition was complete, and heat evolution had ceased, the solution was poured on to cracked ice, and the mixture was shaken vigorously and allowed to separate into two phases. The organic layer was washed with 8% sodium hydroxide (2 × 125 ml), 7% hydrochloric acid (2 × 125 ml) and cold water (100 ml) and dried over anhydrous magnesium sulfate. Filtration, evaporation of the solvent by aspiration at room temperature and then fractional distillation (nitrogen in capillary) gave a clear colorless liquid, which easily crystallized at room temperature to give colorless

* We are indebted to Messrs. General Aniline and Film Corporation for the donation of part of this material.

[20] P. D. Bartlett, F. E. Condon and A. Schneider, *J. Amer. Chem. Soc.* **66**, 1536 (1944).

[21] R. M. Lagidze and N. R. Loladze, *Soobshchenya Akad. Nauk Gruzin. SSR* **16**, 607 (1955); *Chem. Abstr.* **50**, 11960b (1956).

[22] J. G. Smith and G. F Wright, *Canad. J. Chem.* **32**, 729 (1954).

[23] J. E. H. Hancock and D. R. Scheuchenpflug, *J. Amer. Chem. Soc.* In press.

needles of the diacetate, melting at approximately 30–32° (m.p. 28° and 31–32°).[24,25] The above run distilled at 135–135·5°/18 mm (b.p. 106°/3 mm, 122–123°/10 mm);[26,27] n_D^{20} 1·4538 (n_D^{20}1·4547 and 1·4611).[25,27] Yield, 56·0 g, 55 per cent. The poorest yield was 29 per cent and the best 68 per cent; a good yield is usually obtained if heat is evolved during the addition of the acetic anhydride (i.e. cooling should not be too great), and also if redistilled acetic anhydride is used.

Aluminum chloride

This was sublimed under dry nitrogen at 180–200° in a special apparatus, and the sublimed product was sealed off until ready for use. Recovery rarely exceeded 40–50 per cent of the original (crude) chloride, even when reagent-grade material was employed.

Procedure for alkylation[8]

Sublimed aluminum chloride (98·0 g, powdered immediately before use) and benzene (107·0 g, redistilled) were mixed with moderate stirring under nitrogen. The diacetate (61·0 g) of but-2-yne-1,4-diol was added dropwise from a separating funnel: the mixture immediately became orange-red, and slowly changed to a darker red. Evolution of heat was counteracted by cooling to maintain the temperature below 30°. When addition was complete, the separating funnel was replaced by a reflux condenser, calcium chloride tube and a trap for hydrogen chloride. The dark brown mixture was warmed in a water bath at 40–45°, with evolution of hydrogen chloride, and heating at this temperature was continued for 1 hr and then at 80–85° (thermometer in liquid) for 10 hr. The thick dark red liquid was poured into 2 N hydrochloric acid (ca. 1 l.) with cooling below 40°. This mixture was repeatedly extracted with ether, and the extracts were combined, washed with 10% sodium bicarbonate solution and with water, and then dried over anhydrous magnesium sulfate. After the solution had been filtered, volatile matter was removed by evaporation at room temperature, and the residue was distilled *in vacuo* (nitrogen in capillary) through a 6 in. Vigreux column. The fractions obtained were kept under nitrogen at 0° (see Table 2).

TABLE 2.—PRODUCTS OBTAINED FROM THE CONDENSATION OF BUT-2-YNE-1,4-DIOL DIACETATE WITH BENZENE IN PRESENCE OF ALUMINUM CHLORIDE

Fraction	Description	B.p.	Yield (g)
1	Colorless liquid	105–110°/3 mm	34·0
2	Pale green liquid	93–96°/0·15 mm	0·2
3	Pasty green mixture	105–110°/0·1 mm	0·4
4	Cream-colored solid	114–126°/0·1 mm	2·7
5	White solid	129–135°/0·1 mm	0·8
6	Undistillable Dark brown tar		ca. 25

[24] G. Dupont, R. Dulou, et G. Lefèbvre, *Bull. Soc. Chim. Fr.* 816 (1954).
[25] I. M. Gverdtsiteli and Sh. G. Mikadze, *Zh. Obshchei Khim.* **22**, 1401 (1952); *Chem. Abstr.* **47**, 6338f (1953).
[26] W. Reppe *et al.*, *Liebigs Ann.* **596**, 57 (1955).
[27] A. W. Johnson, *J. Chem. Soc.* 1011 (1946).

Fraction 1 solidified to a mass of needles, m.p. ca. 28–31°, on being kept at room temperature, and gave a negative halogen test and hence no 4-acetoxy-1-chlorobut-2-yne was present (compare Lagidze and Petrov,[8] the paper in which this substance was reported). Fractions 4 and 5 were combined and recrystallized twice from ethanol, dissolved in hexane, and chromatographed on alumina (Merck reagent grade, for chromatography: 20 to 1 ratio of alumina to adsorbate). A third crystallization from ethanol provided a total of 0·4 g of pearly plates, melting at 102–103°; yield, 1·1 per cent over-all, or 2·5 per cent if recovered diacetate is taken into account. The crystals fluoresced blue in ultraviolet light, and gave a depression (m.p. 93–96·4°) when mixed with a sample of phenanthrene (m.p. 100°).

2-Phenylnaphthalene (XI)

The method of Elks and Hey[14] was used, with modification. To a stirred cooled mixture of 225 ml of concentrated hydrochloric acid, 250 ml of water and 72 g of 2-naphthylamine, 34·0 g of sodium nitrite was added slowly, the temperature being maintained below 5°. The solution of the diazonium salt was filtered, and then added to a solution of 80·0 g of dimethylamine and 30·0 g of anhydrous sodium carbonate in 150 ml of water. The dark brown solid obtained was filtered off, washed with water and dried in the air (110·0 g). The crude material was purified as follows: the dark brown triazene (20·0 g) was warmed gently with *n*-hexane (350 ml), and the solution was cooled to room temperature and filtered. Some insoluble tan-colored residue (1·8 g, m.p. greater than 200°) remained, and the soluble portion was chromatographed on alumina (as above, for the alkylation product). Hexane eluted 16·6 g of orange solid, m.p. 54–56°, which was crystallized from hexane (1 ml per g) at 0° with 80 per cent recovery per crystallization. After two crystallizations, and washing with ice-cold hexane, 13·2 g of once-chromatographed triazene gave 7·27 g of 1-(2-naphthyl)-3,3-dimethyltriazene as a cream-colored solid, m.p. 56–57° (m.p. 57–58°).[14] The pure triazene becomes orange and red on the surface upon exposure to air, and is best stored under nitrogen.

During the chromatographic purification, several orange-red bands remained on the column, and were only removed by stronger eluting agents. Examination of these substances is in progress.

The purified triazene (5·7 g) was dissolved in benzene (55 ml, reagent grade) and the mixture was heated to boiling. Glacial acetic acid (7·5 ml) was added, and the mixture was heated under reflux for 36 hr (shorter periods gave unchanged triazene). Removal of volatile materials and chromatography as before provided 0·97 g of a pale yellow solid, which was recrystallized from ethanol to give 2-phenylnaphthalene (0·45 g, 13 per cent) as lustrous white plates, m.p. 101·5–102·5° (m.p. 102°).[14] The usual orange-red bands were also recovered from the chromatogram.

Samples of pure alkylation product (m.p. 102–103°) and of the 2-phenylnaphthalene were mixed intimately: this mixture showed no depression of m.p.

Spectral data

The ultraviolet absorption spectra were obtained with a Cary model 11-MS ultraviolet spectrometer: 2-phenylnaphthalene prepared by the alkylation reaction showed λ_{max} 248 and 286 mμ in methyl*cyclo*hexane; ε_{max} 54,000 and 11,000 (λ_{max} 250 and 285 mμ in *cyclo*hexane; ε_{max} 50,000 and 11,000 respectively).[15] Maxima were also detected

at 355 and at 373 mμ; these correspond to the presence of anthracene in concentrations of approximately 0·1–0·5 per cent of the whole. This latter explanation is supported by the fact that in the mass spectrum of the alkylation product there were peaks in the region *m/e* 178, although not of large magnitude. In view of the small amounts at our disposal, no attempt was made to pursue this matter.

The infrared absorption spectra were obtained by using a double-beam infrared spectrometer with a rock-salt optical system, designed and built by L. W. Herscher. The spectra were run in 2 per cent solution in carbon tetrachloride from 2·5–7·5 μ and in 2 per cent solution in carbon disulfide from 7·5–16 μ. Bands were noted at 3·27 (ms), 3·30(m), 6·24(s), 6·66(s), 6·80(m), 6·85(m), 6·97(w), 7·40(w), 7·89(w), 8·83(m), 9·28(m), 9·77(m), 10·40(m), 10·55(m), 11·22(s), 12·23(s), 12·98(s), 13·19(s), 13·52(ms) and 14·37(s) μ(s = strong, m = medium, w = weak).

Mass spectra were obtained using a 90° sector mass spectrometer: a parent peak at *m/e* 204 was noted, plus lower molecular-weight fragments characteristic of a phenylnaphthalene.

Acknowledgements—This research has been facilitated by the kind help of Mrs. V. Krivoshein, Dr. Frank Munk (Reed College) and Mrs. V. Tolkmith (Main Library, The Dow Chemical Company, Midland, Michigan), who rendered willing service in translation. We received invaluable assistance from Dr. J. D. Head (Executive Research) and Mr. W. J. Potts (Spectroscopy Laboratories) of the Dow Chemical Company in obtaining the infrared, ultraviolet and mass-spectrometric data. We wish to express our sincere appreciation to Prof. R. M. Lagidze, Tbilisi State University, Georgia, U.S.S.R., for sending us considerable information, and finally to the Research Corporation of New York for a Frederick Gardner Cottrell grant which defrayed the expenses of this investigation.

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CLAISEN–HAASE REARRANGEMENT OF ENOL ESTERS

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Abstract—The Claisen–Haase rearrangement of β-acyloxyacrylates, RC(O·COR') : CH·CO_2Et, into the isomeric diacylacetates, RCO·CH(COR')·CO_2Et, is subject to base and acid catalysis. The reaction is intermolecular when base-catalysed and probably intramolecular when acid-catalysed.

The related transformation of deoxybenzoin enol esters has also been examined.

CLAISEN AND HAASE[1] discovered the conversion by bases of the enol acetate, ethyl *O*-acetylacetoacetate, into ethyl diacetylacetate and suggested that an intermolecular reaction is involved. Subsequent work[2,3] confirmed that the rearrangement was base-catalysed and intermolecular (mixture experiments), and that it could not be effected thermally. Kästner[4] then showed that the reaction is also acid-catalysed (by boron trifluoride) and postulated, without mixture experiments, an intramolecular migration of the Fries type. Anhydrous ferric chloride has now been found to produce transformation, and a number of β-acyloxyacrylates have been transformed by using various catalysts. The results of the mixture experiments described later (see under "Experimental") suggest that the reaction is, as Kästner[4] stated, intramolecular with acid catalysts (absence of crossed products). Michael and Carlson[3] claimed, however, that metallic sodium converts ethyl *O*-benzoylacetoacetate into ethyl sodioacetylbenzoylacetate by intramolecular migration of the benzoyl group.

In an extension of their previous work, Claisen and Haase[5] found that the acetophenone enol ester, 1-phenylvinyl benzoate, on treatment with a base rearranged into benzoylbenzoylmethane. This type of transformation has also been effected thermally[6] and by acid catalysts.[4,6] Hauser and his colleagues[6] produced evidence that the thermal conversion involves an intramolecular rearrangement and the conversion by boron trifluoride an intermolecular acylation. This latter result is contrary to Kästner's view.

The deoxybenzoin enol esters react less readily. Three esters, 1:2-diphenylvinyl acetate,[7] benzoate and *o*-methoxybenzoate, have been examined in conjunction with base and acid catalysts (sodium hydroxide, potassium hydroxide or sodamide in pyridine; sodium ethoxide in pyridine–ethanol; potassium carbonate in ethyl acetate; sodium in benzene or toluene; boron trifluoride; aluminium chloride). The only successful result was obtained with the benzoate, which with aluminium chloride gave benzoylbenzoylphenylmethane.

[1] L. Claisen and E. Haase, *Ber. Dtsch. Chem. Ges.* **33**, 3778 (1900).
[2] W. Dieckmann and R. Stein, *Ber. Dtsch. Chem. Ges.* **37**, 3370 (1904).
[3] A. Michael and G. H. Carlson, *J. Amer. Chem. Soc.* **57**, 165 (1935).
[4] D. Kästner, Thesis, pp. 29, 66. Marburg; (1937) and *Newer Methods of Preparative Organic Chemistry* p. 289 Interscience, New York (1948).
[5] L. Claisen and E. Haase, *Ber. Dtsch. Chem. Ges.* **36**, 3674 (1903).
[6] F. G. Young, F. C. Frostick, Jun., J. J. Sanderson and C. H. Hauser, *J. Amer. Chem. Soc.* **72**, 3635 (1950).
[7] R. P. Barnes, S. R. Cooper, V. J. Tulane and H. Delaney, *J. Org. Chem.* **8**, 153 (1943).

EXPERIMENTAL

Crystallisation was from ethanol unless otherwise stated.

Rearrangement by acid catalysts

A mixture of ethyl *O*-acetylacetoacetate[8] (1 g), anhydrous ferric chloride (1·1 g) and dry ether (20 ml) was kept for 24 hr, and then treated with dilute hydrochloric acid. Acidification of the alkaline extract of the ethereal layer gave ethyl diacetylacetate as a yellow oil (0·3 g), b.p. 103–104°/16 mm (cupro derivative,[9] m.p. and mixed m.p. 147–148°).

Boron trifluoride was passed at 0° for 1 hr through ethyl *O*-acetylbenzoylacetate[10] in dry ether. The product was added to 30% aqueous sodium acetate at 5–10°. The ethereal solution yielded on treatment with dilute aqueous sodium hydroxide, ethyl acetylbenzoylacetate (70 per cent yield); cupro derivative, m.p. and mixed m.p. 232–234°. (Michael and Carlson[3] give m.p. 232°).

No rearrangement occurred when ethyl *O*-acetylacetoacetate was heated in a sealed Pyrex-glass tube at 320° for 15 min.

Rearrangement by base catalysts

A mixture of ethyl *O*-benzoylacetoacetate[10] (1·2 g), potassium hydroxide (0·5 g) and pyridine (4 ml) was shaken for 18 hr. The product was diluted with water and extracted with ether, before and after acidification. The second ethereal extract was washed with aqueous sodium hydrogen carbonate and with water. When shaken with saturated aqueous copper acetate, it gave the cupro derivative of ethyl acetylbenzoylacetate (0·7 g)[3] (see above).

This rearrangment was also effected in pyridine by potassium carbonate, sodium hydroxide, sodium peroxide and sodium phenoxide. Potassium hydroxide was the most and sodium phenoxide the least satisfactory reagent.

Potassium hydroxide in pyridine was the reagent most usually employed in the experiments described below, although the utility of the other bases mentioned above was also tested. The *C*-acyl derivatives exhibited a red colour with ethanolic ferric chloride.

Preparation of various esters

Ethyl O-(o-*toluoyl*)*acetoacetate*. A mixture of *o*-toluoyl chloride (15 g), ethyl acetoacetate (13 g) and pyridine (15 g) was kept for 2 days. Removal of the solvent from the acid- and alkali-washed ethereal extract gave *ethyl* O-(o-*toluoyl*)*acetoacetate* as a light-yellow oil (14 g), b.p. 148–150°/2 mm (Found: C, 67·8: H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5 per cent). The *O*-acyl derivatives described below were similarly prepared. These compounds do not give a colour with ethanolic ferric chloride.

N-*Phenyl*-N′-o-*toluoylhydrazine*. An ethereal solution of ethyl *O*-(*o*-toluoyl)-acetoacetate (1 g) and phenylhydrazine (0·9 g) was kept at −10° for 12 hr. The *hydrazine* crystallised from aqueous ethanol in needles (0·3 g), m.p. 167° (Found: C, 74·5; H, 6·3. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2 per cent).

[8] L. Claisen and E. Haase, *Ber. Dtsch. Chem. Ges.* **33**, 1242 (1900).
[9] L. Claisen and W. Zedel, *Liebigs Ann.* **277**, 172 (1893).
[10] A. Bernhard, *Liebigs Ann.* **282**, 164 (1894).

Ethyl cuproacetyl-o-toluoylacetate. This ester was prepared from the product of the base-catalysed transformation of the above-mentioned *O*-acyl ester. It separated from benzene in blue needles, m.p. 203–204° (Found: C, 60·2; H, 5·6. $C_{14}H_{15}O_4\frac{1}{2}Cu$ requires C, 60·4; H, 5·4 per cent). This cupro derivative was treated with 10% sulphuric acid and the resulting mixture was extracted with ether. Removal of the solvent gave *ethyl acetyl-o-toluoylacetate* as an oil, b.p. 130–132°/3 mm (Found: C, 68·0; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5 per cent).

Ethyl O-(*o-chlorobenzoyl*) *acetoacetate*. This ester was obtained as a light-yellow oil, b.p. 160–161°/2·5 mm (Found: C, 58·3; H, 4·8; Cl, 13·5. $C_{13}H_{13}O_4Cl$ requires C, 58·1; H, 4·8; Cl, 13·2 per cent).

Ethyl acetyl-o-chlorobenzoylacetate. The *cupro derivative* crystallised in dark-blue cubes, m.p. 217–219° (Found: C, 52·0; H, 4·0; Cl, 11·4. $C_{13}H_{12}O_4Cl\frac{1}{2}Cu$ requires C, 52·1; H, 4·0; Cl, 11·9 per cent). The free ester was obtained as an oil, b.p. 139–140/3 mm (Found: C, 58·4; H, 4·6; Cl, 13·1. $C_{13}H_{13}O_4Cl$ requires C, 58·1; H, 4·8; Cl, 13·2 per cent).

Ethyl O-(p-*chlorobenzoyl*)*acetoacetate*. This ester formed a yellow oil, b.p. 156–157°/3 mm, which solidified to a yellow mass, m.p. 27–31°, when kept at −10° for 3 hr (Found: C, 58·2; H, 4·6; Cl 13·5. $C_{13}H_{13}O_4Cl$ requires C, 58·1; H, 4·8; Cl, 13·2 per cent). *Ethyl acetyl*-p-*chlorobenzoylacetate* was obtained as an oil, b.p. 150–152°/3 mm (Found: C, 58·1; H, 4·7; Cl, 12·6. $C_{13}H_{13}O_4Cl$ requires C, 58·1; H, 4·8; Cl, 13·2 per cent).

Ethyl O-(p-*anisoyl*)*acetoacetate*. This ester separated in micro-crystals, m.p. 46–48° (Found: C, 63·3; H, 6·3. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1 per cent). *Ethyl acetyl*-p-*anisoylacetate* formed a yellow oil, b.p. 160–162°/4 mm (Found: C, 63·6; H, 5·8. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1 per cent).

Ethyl O-(p-*nitrobenzoyl*)*acetoacetate*. This ester separated in micro-crystals, m.p. 83–85° (Found: C, 55·7; H, 4·9; N, 5·0. $C_{13}H_{13}O_6N$ requires C, 55·9; H, 4·7; N, 5·0 per cent). The corresponding *C*-ester crystallised from light petroleum (boiling range 40–60°) in yellow needles, mp. 54–55° (Bülow and Hailer[11] give m.p. 53–55°) (Found: C, 56·2; H, 4·8; N, 4·9. Calc. for $C_{13}H_{13}O_6N$; C, 55·9; H, 4·7; N, 5·0 per cent).

Mixture experiments

(i). Boron trifluoride was passed for 1 hr at 0° through a mixture of ethyl *O*-acetylacetoacetate (2 g) and ethyl benzoylacetate (2·3 g) in dry ether. The product was added to 30% aqueous sodium acetate at 5–10°. The ethereal solution yielded on treatment with dilute aqueous sodium hydroxide an oil (2·2 g), which on fractionation gave:

(*a*) a light-yellow oil (0·4 g), b.p. 94–98°/11 mm (cupro derivative, m.p. and mixed m.p. with ethyl cupro-diacetylacetate,[9] 146–148°);

(*b*) ethyl benzoylacetate, b.p. 146–149°/11mm (cupro derivative, m.p. 180–182°. Wislicenus[12] gives m.p. 182–183°).

Ethyl *O*-acetylacetoacetate (1 g) remained in the ethereal extract of the product.

(ii). When a mixture of ethyl *O*-acetylbenzoylacetate[10] (2·4 g) and ethyl acetoacetate (1·8 g) was treated as described under (*i*), the product consisted mainly

[11] C. Bülow and E. Hailer, *Ber. Dtsch. Chem. Ges.* **35**, 930 (1902).
[12] W. Wislicenus, *Ber. Dtsch. Chem. Ges.* **31**, 3157 (1898).

of ethyl acetylbenzoylacetate with some ethyl acetoacetate. The former was characterised by the cupro derivative, m.p. and mixed m.p.[3] 232–234°.

Deoxybenzoin enol esters

1:2-*Diphenylvinyl benzoate* (*Method* 1). A mixture of deoxybenzoin (25 g) and benzoyl chloride (50 ml) was heated in nitrogen for 10 hr at 180°. Excess of the chloride was evaporated at reduced pressure and an ethereal solution of the residue was de-acidified by aqueous sodium carbonate. The *benzoate* that remained in the solvent separated from ligroin in plates (16 g), m.p. 119° (Found: C, 84·5; H, 5·3. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·4 per cent).

1:2-*Diphenylvinyl benzoate* (*Method* 2). A mixture of deoxybenzoin (5 g), benzoic anhydride (60 g) and sodium benzoate (12 g) was heated at 200° for 4 hr. The product was ground with ice and sodium carbonate and the residue was extracted with boiling water until no more benzoic acid was removed, and was purified in ether as described above. The m.p. of the crystallised product (0·5 g) was not depressed by addition of benzoate prepared by Method 1.

1:2-*Diphenylvinyl* o-*methoxybenzoate*. This was prepared by Method 1. It separated from ethanol in plates, m.p. 88–89° (Found: C, 80·4; H, 5·7; OMe, 10·3. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5; OMe, 9·4 per cent).

Benzoylbenzoylphenylmethane

A mixture of 1:2-diphenylvinyl benzoate (1 g), aluminium chloride (0·6 g) and carbon disulphide (20 ml) was heated under reflux for 15 min., and the solvent was evaporated. The residue was kept at 165° for 15 min and then treated with ice and hydrochloric acid. The product was heated under reflux with ethanol for 8 hr. On cooling, the colourless isomer of benzoylbenzoylphenylmethane separated in plates, m.p. and mixed m.p. with an authentic specimen,[13,14] 148° (Found: C, 83·9; H, 5·4. Calc. for $C_{21}H_{16}O_2$: C, 84·0; H, 5·4 per cent).

Acknowledgements—One of us (N. S. O'C) acknowledges the receipt of a grant from the Medical Research Council of Ireland.

[13] J. Meisenheimer and K. Weibezahn, *Ber. Dtsch. Chem. Ges* **54**, 3205 (1921).
[14] S. Goldschmidt and F. Nagel, *Ber. Dtsch. Chem. Ges.* **63**, 1214 (1930).

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THE FAWORSKII REARRANGEMENT IN THE FORMATION OF 17-METHYL STEROIDS

THE CONFIGURATION OF C-17 BROMIDES*

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(*Received* 23 *September* 1957)

Abstract—The configuration of 17-bromo-20-keto pregnanes and the 17-methyletianic esters have been determined. The Faworskii rearrangement of the former to give the latter has been observed to be abnormal. It is suggested that C-17 → C-21 halogen transfer intervenes.

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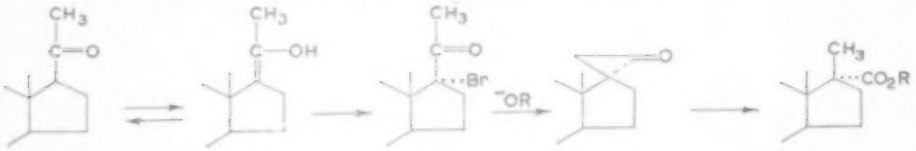
THE formation of 17-methyl etianates by Faworskii rearrangement of 17-bromo-20-keto steroids has been effected in a large number of cases.[1–4] In all instances the structure of the major product has been formulated as a 17α-methyl etianate principally on the basis of molecular rotation evidence and activity correlations.[5]

A consideration of the mechanics of the Faworskii rearrangement as set forth by the tracer work of Loftfield[6] suggested that the steroid acids should have a 17β-oriented methyl group. This conclusion was based on the assumption that bromination of a 20-keto steroid by way of its $\Delta^{17(20)}$-enol should, in keeping with all precedent, follow the rule-of-the-rear[7] and yield a 17α-bromo-20-keto product. Ensuing Faworskii rearrangement with attending inversion at C-17 in the formation of an intermediate *cyclo*propanone should, in its ultimate phase, yield a 17β-methyl etianate, thus,



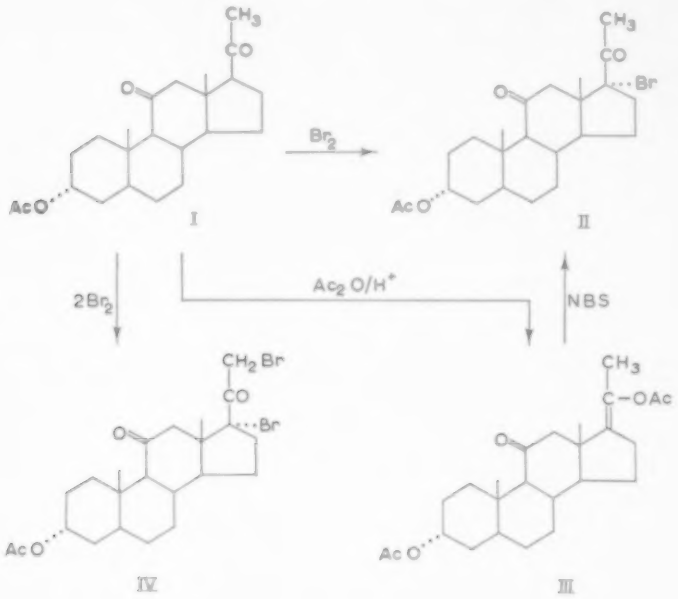
In view of these considerations it was felt that chemical substantiation for the configuration of the 17-methyl Faworskii products would be desirable and further that their formation from a 17-bromo-20-keto pregnane of known stereochemistry should be sought.

The direct bromination of 3α-acetoxy pregnane-11,20-dione (I) has been reported recently by Engel to give a 17-bromo derivative, m.p. 168–170° of unknown configuration.[8] By treatment of the enol acetate derivative of I with N-bromsuccinimide, the Upjohn group[9,10] has also prepared in superior yield a 17-bromo derivative, m.p. 175–176°, which appeared to be the same as the product of direct bromination.[8]

* For a preliminary account of this work see: N. L. Wendler, R. P. Graber and G. G. Hazen, *Chem. Ind. (Rec.)* 847 (1956).

[1] R. E. Marker and R. B. Wagner, *J. Amer. Chem. Soc.* **64**, 216 (1942); **64**, 1273 (1942).
[2] Pl. Plattner, H. Heusser and S. E. Boyce, *Helv. Chim. Acta* **31**, 603 (1948).
[3] Pl. Plattner, H. Heusser and P. Th. Herzig, *Helv. Chim. Acta* **32**, 270 (1949).
[4] H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. Plattner, *Helv. Chim. Acta* **33**, 2229 (1950).
[5] Ch. R. Engel and G. Just, *J. Amer. Chem. Soc.* **76**, 4909 (1954).
[6] R. B. Loftfield, *J. Amer. Chem. Soc.* **73**, 4707 (1951).
[7] T. F. Gallagher and T. H. Kritchevsky, *J. Amer. Chem. Soc.* **72**, 882 (1952).
[8] Ch. R. Engel, *J. Amer. Chem. Soc.* **78**, 4727 (1956).
[9] H. V. Anderson, E. R. Garrett, F. H. Lincoln, A. H. Nathan and J. A. Hogg, *J. Amer. Chem. Soc.* **76**, 743 (1954).
[10] B. J. Magerlein, D. A. Lyttle and R. H. Levin, *J. Org. Chem.* **20**, 1709 (1955).

We have repeated the above procedures and have found that the bromo derivatives obtained by the direct as well as the indirect method are indeed identical by mixed m.p. and infrared comparison. Further, it has been established that this 17-bromo derivative is a single individual by paper partition chromatography. In the latter connection dimethyl formamide was employed as the stationary phase and a 3 : 1 mixture of *cyclo*hexane in benzene as the mobile phase; the iodine-vapor technique[11] was used in tracing the compound. By this procedure 11-ketoprogesterone and 11-keto-17-*iso*progesterone as well as 11β-hydroxy progesterone and 11β-hydroxy-17-*iso*progesterone were found to be clearly and distinctly resolved.

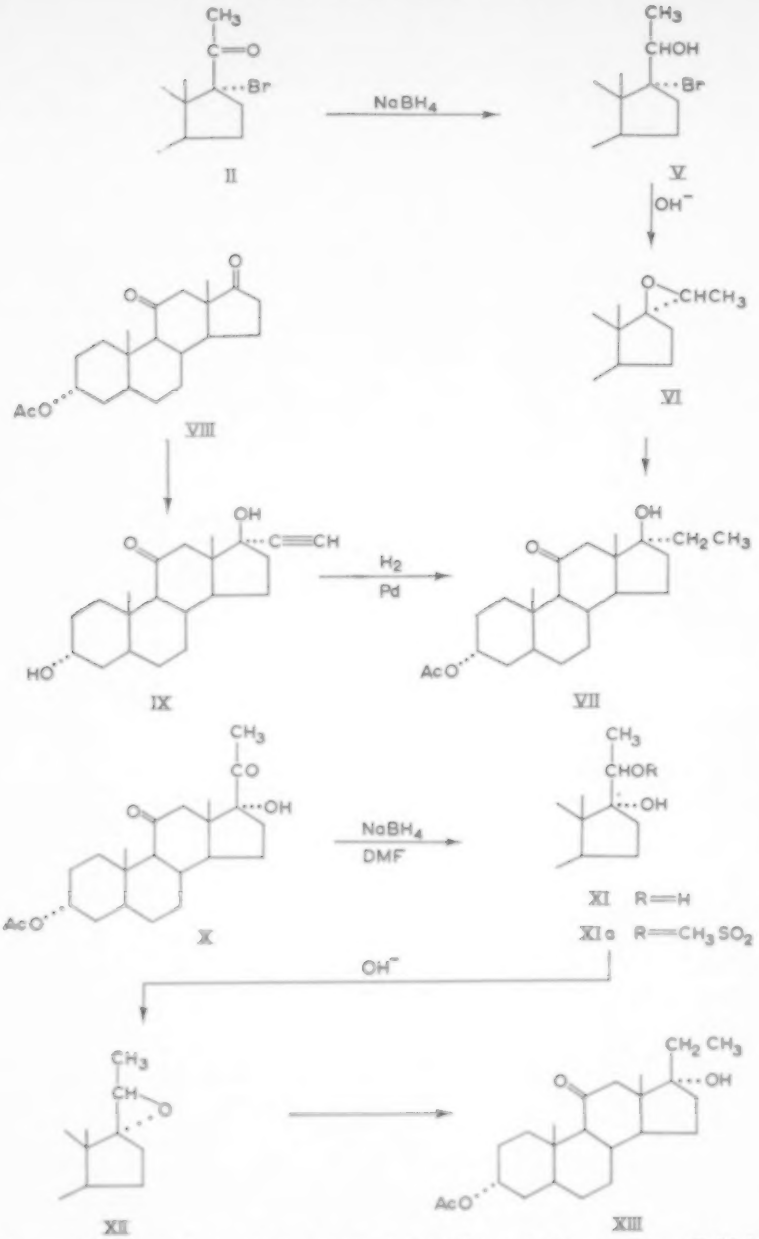


The configuration of the bromine substituent of II was established as being 17α in the following manner: II was reduced at C-20 by means of sodium borohydride; the resultant bromohydrin without isolation was converted by alkali with attending inversion at C-17 to the β-oxide (VI) and thence to 3α-acetoxy-17β-hydroxy-17-*iso*pregnane-11-one (VII) by successive reduction with lithium aluminum hydride, acetylation at C-3 and reoxidation at C-11. The carbinol VII thus produced was identical with an authentic sample prepared from 3α-acetoxyetiocholane-11,17-dione VIII with ethylmagnesium bromide or sodium acetylide followed by hydrogenation and acetylation.

The reduction of II → V was accompanied by considerable reductive loss of bromine to give as a by-product the corresponding C-20-hydroxy compound; the latter was identical with the corresponding C-20-reduction ($NaBH_4$) product of I.

The C-17-isomer of VII, namely XIII, was synthesized as a reference compound since its formation as a consequence of the above sequence would have been the case had the configuration of II been reversed at C-17. 3α-Acetoxy-17α-hydroxypregnane-

[11] G. B. Marini-Bettolo-Marconi and S. Guarino, *Experientia* **6**, 309 (1950).



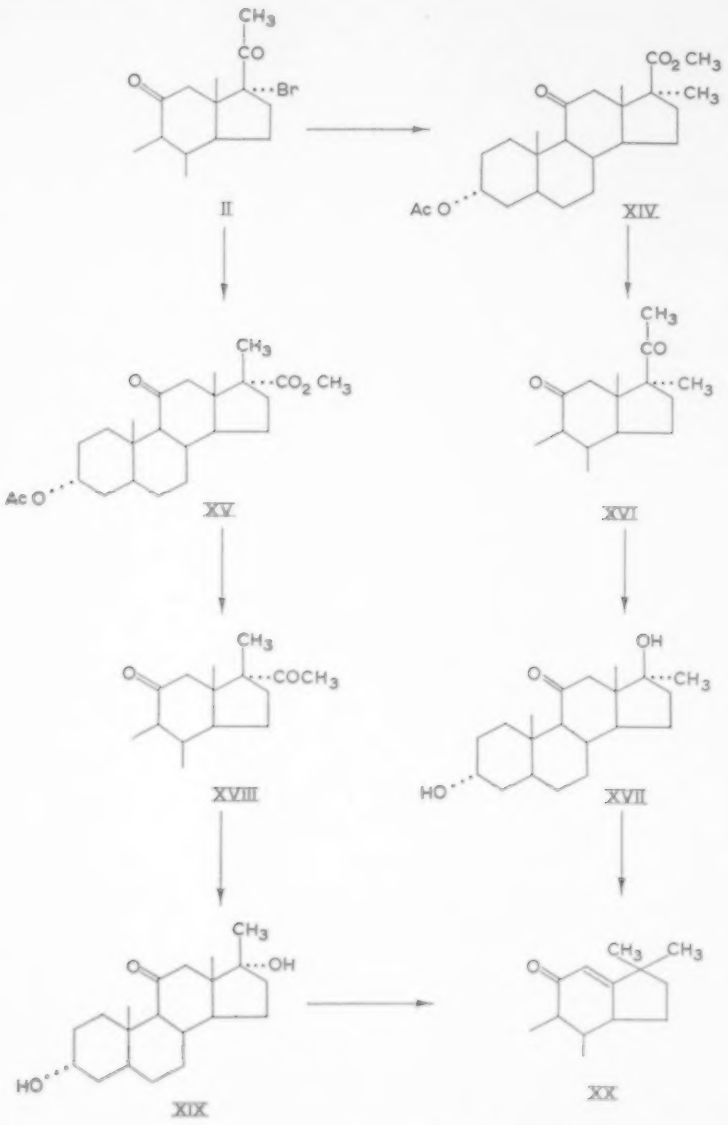
11,20-dione (X) was selectively reduced at C-20[12*] and the resulting C-20-hydroxy derivative (XI) in the form of its mesylate derivative (XIa) was converted to the α-oxide (XII) by means of sodium methoxide. Reductive scission of the oxide function

* Reductions carried out at room temperature with sodium borohydride in aqueous dimethyl formamide have been found to be highly specific, enabling e.g. the reduction of 20-CO in the presence of Δ^4-3-CO and 11-CO as well as a 21-acetoxyl function.

[12] D. Taub, R. D. Hoffsommer and N. L. Wendler, *Abstracts of papers* p. 23. 132nd Meeting of the American Chemical Society, New York, Sept. 8–13 (1957).

with lithium aluminum hydride followed by acetylation at C-3 and reoxidation at C-11 provided XIII in good overall yield.

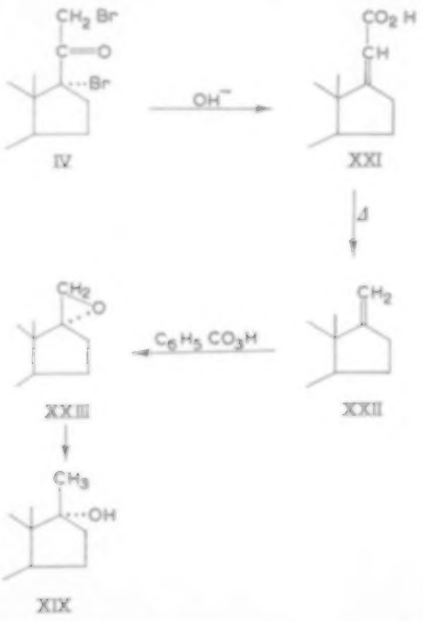
The Faworskii rearrangement of the 17α-bromoketone (II) was effected by refluxing with excess 3% sodium methoxide in methanol for 2 hr. The product was acety-



lated and chromatographed to yield ca. 60 per cent of the 17α-methyl etianate (XIV) and ca. 40 per cent of the 17β-methyl etianate (XV). The configuration of these esters was determined in the following manner: The 17α-methyl ester (XIV) was converted by saponification and acetylation to the corresponding 3α-acetoxy acid; the latter by

way of its acid chloride on treatment with diazomethane followed by hydrogen chloride and reduction with zinc afforded the methyl ketone (XVI).* Oxidation of XVI with peroxytrifluoroacetic acid[13] with subsequent saponification yielded 3α,17β-dihydroxy-17α-methyletiocholane-11-one (XVII) identical with authentic material prepared from 3α-acetoxyetiocholane-11,17-dione VIII with methylmagnesium iodide.†

In a similar manner the 17β-methyl ester (XV) was converted to the methyl ketone (XVIII) and thence with peroxytrifluoracetic acid and subsequent saponification to 3α,17α-dihydroxy-17β-methyletiocholane-11-one (XIX). An authentic sample of XIX was prepared by the method of Sondheimer *et al.*[14] in the following manner: Bromination of 3α-acetoxypregnane-11,20-dione (I) with 2 moles of bromine afforded the known 17,21-dibromide (IV).‡ Faworskii rearrangement of IV gave the unsaturated acid XXI which was decarboxylated to the olefin XXII. The latter was successively epoxidized with perbenzoic acid and reduced with lithium aluminum hydride according to the method of Sondheimer *et al.*[14] The product thus obtained was acetylated at C-3 and oxidized at C-11 followed by removal of the 3-acetate function to give XIX. The two samples of XIX prepared from XV and IV were found to be identical.



Both epimeric carbinols XVII and XIX were found to undergo the Kägi–Miescher rearrangement[15] to give the $\Delta^{\alpha,\beta}$ketone XX. Therefore the rearrangement to form XX is not dependent on the configuration at C-17 with the tertiary carbinols XVII and XIX in the manner found to be the case with the C-17-secondary carbinols.[15]

* Method of Pl. Plattner *et al.* (reference 3) has been used.

† When VIII was treated with excess methylmagnesium iodide at 65° an appreciable quantity of product was obtained which in all probability corresponds to reaction at both the C-11 and C-17 carbonyls. See Experimental.

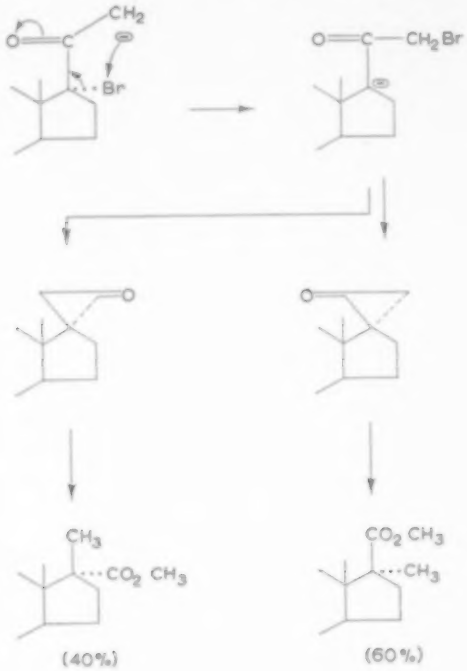
‡ Ch. Engel (reference 8) isolated this dibromide as a minor product from the preparation of II.

[13] W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.* **77**, 2287 (1955).

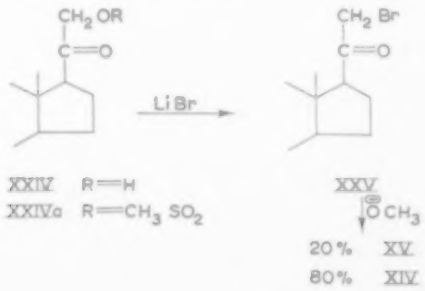
[14] F. Sondheimer, O. Mancera, M. Urquiza and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 4145 (1956).

[15] H. Kägi and K. Miescher, *Helv. Chim. Acta* **22**, 683 (1939); **32**, 761 (1949).

As a consequence of the above transformations, the configurations of the 17-bromo and 17-methyl pregnane derivatives have been placed on a firm basis, thereby permitting certain conclusions with regard to the *modus operandi* of the Faworskii rearrangement as applied to these systems. It has been seen that starting with a stereochemically pure 17α-bromo-20-keto steroid, the major product arising from Faworskii rearrangement is not the product to be expected from transformation according to the mechanism established by Loftfield.[6] Consequently it is suggested that the Faworskii change in the case of 17α-bromo-20-keto steroids is preceded by a bromine transfer from C-17 → C-21 to give a configurationally independent species capable of providing



either isomeric ester by way of its appropriate *cyclo*propanone precursor. As previously pointed out the ratio of 17β-methyl ester (XV) to 17α-methyl ester (XIV) formed from II is ca. 40 : 60. It has been shown further, however, that the Faworskii rearrangement of 3α-acetoxy-21-bromopregnane-11,20-dione (XXV) yields XV and



XIV in a ratio not greater than 20 : 80.* Therefore, it reasonably follows that the 17α-bromo-20-ketone (II) is capable of rearranging normally in a direct sense to the extent of at least 20 per cent.

These findings indicate that the act of bromine displacement leading to the appropriate *cyclo*propanone intermediate in the Faworskii change proceeds with greater facility in the geometrically α-sense, a consequence which is in agreement with expectations based on steric considerations.

EXPERIMENTAL

3α-Acetoxy-17α-bromopregnane-11,20-dione (II)

(a) Prepared by direct bromination of 3α-acetoxypregnane-3,11-dione (I) according to Engel;[8] crystallized from ether m.p. 168–71° (in reference 8 m.p. 168–70°).

(b) Prepared by treatment of the $\Delta^{17(20)}$-enol acetate derivative of 3α-acetoxypregnane-11,20-dione (III) with N-bromsuccinimide according to Anderson *et al.*[9] Crystallized from acetone m.p. 174–5° (in reference 9 m.p. 175–6°).

Samples of II prepared by methods (a) and (b) were not depressed on mixed melting point determination and were shown to have identical infrared spectra. A sample of II was submitted to paper-strip chromatography employing dimethyl formamide as the stationary phase and a 3 : 1 mixture of *cyclo*hexane and benzene as the mobile phase. The compound was traced by the iodine vapor technique[11] as well as by 2,4-dinitrophenyl hydrazine reagent subsequent to u.v. irradiation and found to be a single spot. As a control, 11-ketoprogesterone and 11-keto-17-*iso*progesterone were found to be cleanly and distinctly resolved in this system. Likewise 11β-hydroxyprogesterone and 11β-hydroxy-17-*iso*progesterone were unambiguously separated to give a two-spot paper chromatogram.

Conversion of 3α-acetoxy-17α-bromopregnane-11,20-dione (II) *to 3α-Acetoxy-17β-hydroxy-17-iso*pregnane-11-one (VII)

A solution of 1·18 g of bromo derivative (II) (m.p. 174–5°) in 40 cm³ of tetrahydrofuran and 40 cm³ of methanol was treated with 100 mg of sodium borohydride and allowed to stand at room temperature for 1 hr. At the end of this period 0·75 cm³ of acetic acid was added and the reaction mixture evaporated to dryness. The product was extracted with ethyl acetate and the ethyl acetate extract washed with distilled water. Analysis of the aqueous layer revealed ionic bromine corresponding to reductive loss of bromine from II. Since the residue obtained on evaporation of the organic layer still gave a positive test with 2,4-dinitrophenylhydrazine reagent, indicating unreduced 20-carbonyl, this material was resubjected to reduction as before with 100 mg of sodium borohydride to give a product no longer exhibiting a positive reaction with 2,4-dinitrophenylhydrazine reagent.

The above reduction product (1 g) was dissolved in 30 cm³ of methanol, treated with 1 g of potassium hydroxide in 3 cm³ of water and 7 cm³ of methanol and allowed to stand at room temperature for 2 hr. The reaction mixture was evaporated to dryness and extracted with ethyl acetate to give 0·8 g of halogen-free product containing VI.

* Faworskii rearrangement of 21-halogenated 20-keto steroids was first carried out by Pl. Plattner, H. Heusser and S. E. Boyce (reference 2) and shown by these authors to be superior to the 17-bromo systems in the production of what is now established as being the 17α-methyl isomer.

The above product from base treatment (0·8 g) containing VI was dissolved in 90 cm³ of tetrahydrofuran, treated with 1 g of lithium aluminum hydride and refluxed for 3 hr. At the end of this time the excess lithium aluminum hydride was destroyed by dropwise addition of 5 cm³ ethyl acetate and finally 20 cm³ of saturated sodium sulfate solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was acetylated at room temperature with acetic anhydride in pyridine and the acetylated product oxidized with 230 mg of chromic anhydride in 25 cm³ of glacial acetic acid. The crude oxidation product was chromatographed on 50 g of acid-washed alumina and eluted with benzene–ether mixtures to give ca. 600 mg of 3α,20-diacetoxypregnane-11-one identical by infrared comparison with material obtained from I by reduction with sodium borohydride in aqueous dimethyl formamide at C-20, followed by acetylation. The fractions eluted with 20% and 50% ether in benzene corresponded to ca. 80 mg of 3α-acetoxy-17β-hydroxy-17-*iso*pregnane-11-one (VII) m.p. 203·5–205·5°. This material was not depressed in m.p. on admixture with an authentic sample of VII (see below) and was identical with it by infrared spectral comparison.

Synthesis of 3α-*acetoxy*-17β-*hydroxy*-17-iso*pregnane*-11-*one* (VII) *from* 3α-*acetoxyetiocholan*-11,12-*dione* (VIII)*

A 5 g sample of 17-ketone (VIII) was ethinylated according to the method of Stavely[16] as adapted by Sarett[17] to give 4·1 g of 17α-ethinyletiocholane-3α,17β-diol-11-one (IX) m.p. 210–15°. Crystallized from ethyl acetate m.p. 214–16° (in reference 17 m.p. 218·5–219°).

The above ethinyl carbinol (330 mg) was hydrogenated in 10 cm³ of absolute ethanol at 1 atm and 24°C, with 50 mg of 10% palladium-on-charcoal catalyst. The calculated uptake (2 moles) of hydrogen was complete in 40 min. The product was isolated and acetylated with acetic anhydride in pyridine at room temperature and the acetylated product crystallized from acetone–ether m.p. 203–6°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73·35; H, 9·64. Found: C, 73·56; H, 9·57.

The same substance (VII) was obtained in inferior yield by reaction of VII with ethyl magnesium bromide followed by acetylation.

3α-*Acetoxy*-17α,20-*oxidopregnane*-11-*one* (XII)

A solution of 5 g of 3α-acetoxy-17α-hydroxypregnane-11,20-dione (X) in 125 cm³ of dimethyl formamide was treated with 1·25 g of sodium borohydride in 12·5 cm³ of water and the reaction mixture allowed to stand for 1 hr at room temperature. At the end of the period the excess sodium borohydride was decomposed by cautious addition of acetic acid with cooling. The product was precipitated by addition of water and extracted with ether. The ether extract was evaporated to a foam and treated overnight at 0–5° with 2·5 cm³ of methanesulfonyl chloride in 10 cm³ of pyridine. The crude mesylate derivative was dissolved in 500 cm³ of warm methanol and treated with 15 g potassium hydroxide in 30 cm³ water for 2 hr at room temperature. At the end of this period the methanol was evaporated *in vacuo* and the residue extracted with ether–ethyl acetate. An aliquot of the product was chromatographed. The

* Performed by H. L. Slates of these Laboratories.

[16] H. Stavely, *J. Amer. Chem. Soc.* **61**, 79 (1939).
[17] L. H. Sarett, *J. Biol. Chem.* **162**, 601 (1940).

fractions eluted with benzene and 10% ether in benzene afforded XII as colorless, transparent prisms from ether which on melting lose solvent of crystallization at 80° and undergo a phase change at 112° producing needles that melt at 128–9°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73·80; H, 9·10, Found: C, 74·01; H, 9·00.

Later fractions from the chromatogram yielded 3α,20-diacetoxy-17α-hydroxypregnane-11-one, m.p. 244–46·5°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69·44; H, 8·33. Found: C, 69·72; H, 8·76.

3α-Acetoxy-17α-hydroxypregnane-11-one (XIII)

In the conversion of the oxide XII to the pregnane derivative XIII it was found unnecessary to purify by chromatography at that stage. Therefore the crude oxide obtained above by alkali treatment of its mesylate precursor was reduced with 2·5 g of lithium aluminum hydride in 200 cm³ of refluxing tetrahydrofuran for 3 hr. The product was worked up as described previously, acetylated with acetic anhydride in pyridine and the acetylated product oxidized in 50 cm³ of acetic acid with 1 g of chromium trioxide. The crude oxidation product on chromatography afforded 1·85 g of 3α-acetoxy-17α-hydroxypregnane-11-one (XIII), m.p. 147·5°, $\lambda_{max}^{CCl_4}$ 2·82 μ (OH); 5·79 μ (OAc); 5·87 μ (C=O).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73·40; H, 9·57. Found: C, 73·37; H, 9·52.

Later fractions from the chromatography again produced 3α,21-diacetoxy-17α-hydroxypregnane-11-one as experienced at the purification stage of this oxide (XII) (see above).

Methyl 3α-acetoxy-11-keto-17α-methyletianate (XIV) *and methyl 3α-acetoxy-11-keto-17β-methyl-17-isoetianate* (XV). *Faworskii rearrangement of 3α-acetoxy-17α-bromopregnane-11,20-dione* (II)

To a solution of 1 g of sodium metal in 30 cm³ of methanol was added 1 g of purified bromoketone (II), m.p. 172–173·5°. The reaction mixture was refluxed for 3·5 hr. At the end of this period the methanol was evaporated *in vacuo* and the product dissolved in ethyl acetate–water. The ethyl acetate solution was dried and concentrated to dryness. The residue was acetylated with 2 cm³ of acetic anhydride in 2 cm³ of pyridine and a 700 mg sample of the acetylated product chromatographed on 35 g of acid-washed alumina. The eluates corresponding to 20–50% benzene in petroleum ether afforded 236 mg (40 per cent) of methyl 3α-acetoxy-11-keto-17β-methyl-17-*iso*etianate (XV) as long needles from ether–petroleum ether, m.p. 156–7° $[\alpha]_D^{25}$ +46° (1·0 chf.).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71·25; H, 8·99. Found: C, 71·63; H, 8·95.

The eluates corresponding to benzene and 5% ether in benzene afforded 361 mg (60 per cent) of methyl 3α-acetoxy-11-keto-17α-methyletianate (XIV) as plate-like prisms from ether m.p. 168–70° with phase change to form massive prisms, m.p. 182–4°, $[\alpha]_D^{CHCl_3}$ +62 (in reference 8 m.p. 184° $[\alpha]_D^{25°}$ +63·7°(chf.)).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71·25; H, 8·99. Found: C, 71·17; H, 8·80.

The eluates (50% benzene in petroleum ether–benzene) representing overlap fractions of XIV and XV amounted to 92 mg were shown by infrared analysis to consist of essentially equal amounts of the two isomers.

A Faworskii rearrangement carried out on 21·3 g of bromoketone (II), m.p. 168·5–172°, afforded after due processing 7·3 g of XV and 8·6 g of XIV.

3α-Hydroxy-11-keto-17α-methyletianic acid

The total crude amorphous residue from the bromination of 50·0 g (0·134 mole) of pregnane-11,20-dione-3α-ol 3-acetate with 21·5 g (0·135 mole) of bromine in a mixture of chloroform and methanol was treated with 1·4 l. of methanolic sodium methoxide containing 12·5 g (0·231 mole) of sodium methoxide. The mixture was heated under reflux for 3 hr, cooled and a cold solution of 240 g (4·28 moles) of potassium hydroxide in 300 ml of water added. Reflux was continued for an additional 40 hr, concentrated *in vacuo* to 300 ml and diluted with 400 ml of water. The insoluble gum which separated was removed by extraction with 2 portions of chloroform. The aqueous layer was filtered through Supercel and then acidified with 2 N hydrochloric acid. The precipitated acid was removed by filtration, washed with water and dried, weight 28·0 g (59·9 per cent), m.p. (cap.) 210–240°. Recrystallization from acetone afforded 13·9 g (29·7 per cent), m.p. (cap.) 280–281·5°, $[\alpha]_D^{25}$ +36° (1·0, dioxane) (in reference 8 m.p. 285–286°, $[\alpha]_D^{25}$ +29·5° (1·0, dioxane)); an additional recrystallization did not raise the m.p. An additional 2·5 g was obtained from the mother liquors to bring the total yield to 35 per cent.

Hydrolysis of the 17α-methylacetoxy ester (XIV) with refluxing aqueous methanolic potassium hydroxide as described below for the hydrolysis of the 17β-methyl ester (XV) gave material m.p. (cap.) 280–282°, undepressed on admixture with that prepared above.

The corresponding *methyl ester* was prepared by treating a slurry of 400 mg of the acid above in 20 ml of ether with excess ethereal diazomethane. The solid dissolved and nitrogen was evolved. Evaporation of the solvent and recrystallization from ether gave material, m.p. (cap.) 163·5–165°, $[\alpha]_D^{25}$ +42° (1·0, $CHCl_3$) (reference 8 m.p. 165°, $[\alpha]_D^{22}$ +41·5° (1·01, $CHCl_3$)).

17α-Methylpregnane-11,20-dione-3α-ol 3-acetate (XVI)

A solution of 2·0 g of the 17α-methyl acid, m.p. (cap.) 278–280°, in 10 ml of pyridine and 4·3 ml of acetic anhydride was heated for 1 hr at 70°, then 5 ml of water added and heating continued at 45° for an additional hour. The solution was poured into 200 ml of ice water, and acidified with concentrated hydrochloric acid. The colorless crystalline precipitate was removed by filtration, washed thoroughly with water and dried, weight 2·2 g (93·7 per cent), m.p. (cap.) 254–260°. One recrystallization from acetonitrile gave 1·7 g of *3α-acetoxy-11-keto-17α-methyletianic acid*, m.p. (cap.) 262–264·5°, $[\alpha]_D^{25}$ +58° (1·0 $CHCl_3$). Further recrystallization did not raise the m.p.

A 1·0 g sample of the acetoxy acid above in 25 ml of dry benzene was cooled to 10° and 4·0 ml of oxalyl chloride added. The solution was allowed to warm to room temperature for 2 hr and then heated briefly under reflux. Concentration *in vacuo* gave a crystalline residue which was dissolved in 20 ml of ether and reconcentrated. Recrystallization from ether afforded 0·7 g (66·8 per cent) of 3α-acetoxy-11-keto-17α-methyletianic acid chloride, m.p. (cap.) 189–192°.

Anal. Calcd. for $C_{23}H_{33}O_4Cl$: Cl, 8·67. Found: Cl, 8·62.

An ethereal solution of diazomethane was prepared from 2·5 g of N-nitroso-N-methylurea. This solution was added to an ice cold solution of 1·0 g of the acid chloride above in 10 ml of dry benzene and 20 ml of dry ether and the mixture stored at 0° for 15 hr. Then 20 ml of ether was distilled and after cooling to 0°, a solution of

0·5 g of hydrogen chloride in 10 ml of ether added. The evolution of nitrogen ceased in 0·5 hr. The excess acid was removed by washing with dilute aqueous sodium bicarbonate, the solution dried over sodium sulfate, filtered and the solvents removed *in vacuo* to give a brown gummy residue. Crystallization from acetonitrile afforded 0·40 g (38·5 per cent) of 21-*chloro*-17α-*methylpregnone*-11,20-*dione*-3α-*ol* 3-*acetate*, m.p. (cap.) 165–175°.

Anal. Calcd. for $C_{24}H_{35}O_4Cl$: Cl, 8·38. Found: Cl, 8·41.

Reductive removal of the 21-chlorine was carried out as follows: A solution of 2·0 g of the 17α-methyl chlorketone in 20 ml of glacial acetic acid was warmed to 40° and 2·0 g of zinc dust added portion-wise. After 1 hr, 100 ml of water was added and the precipitate collected on a filter, washed with water and dried, m.p. (cap.) 150–185°. A solution of this product in 40 ml of 1 : 1 benzene–hexane was poured into a column of 40 g of acid-washed alumina (Harshaw chromatographic grade). Elution with 2 l. of 1 : 1 benzene–hexane gave 1·1 g (59·8 per cent) of the 17α-methylpregnane (XVI), m.p. (cap.) 187–190°. Recrystallization from acetone, then from ethyl acetate, raised the m.p. (cap.) to 189·5–191°. The infrared spectrum in the solid state exhibited bands at 5·74 and 5·85 μ indicating the presence of acetate and carbonyl functions.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74·23; H, 9·28. Found: C, 74·18; H, 9·28.

When the preparation of XVI was carried out without isolation of the 21-chloro compound a 43 per cent yield was obtained from the acid chloride.

3α,17β-*Dihydroxy*-17α-*methyletiocholane*-11-*one* (XVII)

(*a*) *Via peroxytrifluoroacetic acid oxidation of* XVI. To a mixture of 0·41 ml of 90% hydrogen peroxide and 2·5 ml of methylene chloride at 0° was added with stirring 2·54 ml of trifluoroacetic anhydride over a period of 18 min. After about half of the anhydride had been added, the mixture became a single phase. The mixture was stirred for a few minutes more and then transferred to a dropping funnel and added dropwise with stirring to an ice-cold solution of 388·5 mg 17α-methylpregnane-11,20-dione-3α-ol 3-acetate (XVI) in 7·5 ml of methylene chloride containing 6·5 g of disodium hydrogen phosphate. The addition required 10 min and at the end, the slurry had become very thick. After an additional 10 min, the mixture was allowed to warm to 25° and stirring continued for 2 hr. During this time, considerable frothing was observed and 30 ml of methylene chloride was added in 3 portions at intervals. Finally, the mixture was heated under reflux for ½ hr, then 50 ml of water was added to dissolve the salts. The mixture was shaken vigorously, separated, and the aqueous layer extracted with an additional 25 ml of methylene chloride. The combined methylene chloride extracts were washed once with saturated salt solution, filtered through anhydrous magnesium sulfate and the solvent removed *in vacuo* to give 405 mg of colorless crystalline residue, m.p. (micro) 158–178° with previous softening. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 212·6 mg of crystals, m.p. (micro) 168–175°; the m.p. on admixture with the starting material (XVI) was 170–189°.

Since the product appeared to be a mixture, it was combined with its mother liquor and concentrated to dryness. The residue was heated under reflux for 2 hr and 40 min with 20 ml of methanol and 10 ml of 30% aqueous potassium hydroxide. The methanol was removed *in vacuo*, 25 ml of water added, and the product extracted with 4 portions of chloroform. The combined extracts were washed with water until

neutral, then filtered through magnesium sulfate and the solvent removed *in vacuo* to give 270 mg of amorphous solid. This material was chromatographed over 13·5 g of neutral alumina. The fractions eluted with benzene, 10%, 20% and 50% ether in benzene weighed 165 mg and crystallized as needles upon addition of ether. A portion of this material was recrystallized from ether–petroleum ether (b.p. 30–60°) and had the m.p. (micro) 76–81° with evolution of gas, resolidification as prismatic needles, remelting 130–133°, resolidification as plates, remelting 146–148·5°. This material was shown to be 17α-methylpregnane-11,20-dione-3α-ol by acetylation of a sample with acetic anhydride and pyridine for 5 hr at 100°. The product, after one recrystallization from ether–petroleum ether (b.p. 30–60°), had the m.p. 189–190·5°, undepressed on admixture with the starting material (XVI).

The fractions eluted with ether, 10% acetone–ether and with acetone crystallized spontaneously as prisms. These fractions were combined, weight 48 mg, and recrystallized twice from acetone–ether–petroleum ether (b.p. 30–60°) to give prisms, m.p. (micro) 203·5–205·5°, undepressed on admixture with 3α,17β-dihydroxy-17α-methyletiocholane-11-one prepared in part B below. The identity was confirmed by infrared comparison.

(b) *Via the reaction of methylmagnesium iodide with* 3α-*acetoxyetiocholane*-11,17-*dione* (VIII). Methylmagnesium iodide was prepared from 2·4 g of magnesium and 20 g of methyl iodide. The ether was distilled off and replaced with benzene until the temperature reached 60°. To the resulting solution of methylmagnesium iodide was added 1·75 g of 3α-acetoxyetiocholan-11,17-dione and the homogeneous solution was refluxed 2 hr. The reaction product was worked up by hydrolysis with water and ammonium chloride, acetylated and chromatographed. The eluates consisting of 1–5% ether in benzene afforded what is probably slightly impure 11α,17α-*dimethyletiocholane* 3α,11β,17β-*triol* 3-*acetate** as needles m.p. 140–2°, λ_{max} 2·95 μ (OH), 5·8 μ (OAc), 5·84 μ (very weak).

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 73·02; H, 10·05. Found: C, 73·15; H, 9·73.

The eluates representing 10—20% ether in benzene afforded 3α-*acetoxy*-17β-*hydroxy*-17α-*methyletiocholane*-11-*one* as prisms m.p. 210–13°. λ_{max} 2·92 μ (OH), 5·8 μ (OAc), 5·86 μ (C=O).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72·93; H, 9·46. Found: C, 73·25; H, 9·35.

A solution of 135 mg of the above 3α-acetoxy-17β-hydroxy-17α-methyletiocholone-11-one in 10 cm³ of methanol was refluxed for 2 hr with 1 g of potassium hydroxide in 1 cm³ of water. The product was crystallized from acetone–hexane to give 3α,17β-*dihydroxy*-17α-*methyletiocholane*-11-*one*, m.p. 203–5°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 75·00; H, 10·00. Found: C, 75·15; H, 9·81.

This material was found to be identical with that obtained in Part A above by mixed m.p. and infrared comparison.

3α-*Hydroxy*-11-*keto*-17β-*methyl*-17-iso*etianic acid*

A solution of 4·85 g (12·0 mmoles) of the 17β-methyl ester (XV), m.p. 156–7°, in 242·5 ml of 10% methanolic potassium hydroxide was heated in a nitrogen atmosphere at 170° for 48 hr in a glass-lined hydrogenation bomb. The methanol was then removed *in vacuo*, 450 ml of water added and the solution extracted with 3 portions of ether which were discarded. The aqueous layer was acidified with 80 ml of 6 N

* See footnote (†) p. 148.

hydrochloric acid and the solid which separated extracted with 3 portions of ethyl acetate. The combined extracts were washed 4 times with water, once with saturated salt solution, filtered through anhydrous magnesium sulfate and the solvent removed *in vacuo* to give 4·325 g of light brown crystalline residue. Recrystallization from ethyl acetate gave 3·18 g (76 per cent) of prisms, m.p. (micro) 260–263°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72·30; H, 9·26. Found: C, 71·93; H, 9·31.

The hydrolysis of the 17β-methyl ester (XV) was also carried out by hydrolysis with aqueous methanolic potassium hydroxide. A solution of 400 mg of XV in 40 ml of methanol was mixed with a solution of 6 g of potassium hydroxide in 7·5 ml of water. The mixture was heated under reflux for 48 hr, concentrated *in vacuo* to 7 ml, diluted with 10 ml of water and acidified with 2 N hydrochloric acid. The crystalline precipitate was filtered, washed with water and dried, m.p. (cap.) 255·5–259°. Recrystallization from acetonitrile raised the m.p. (cap.) to 258–259·5°.

17β-*Methyl*-17-iso*pregnane*-11,20-*dione*-3α-*ol* 3-*acetate* (XVIII).

A 2·09 g (6·0 mmole) sample of the 17β-methyl acid was treated with 10 ml of pyridine and 10 ml of acetic anhydride. After standing at 25° for 3 hr, the excess reagents were removed *in vacuo*. The residual oil was dissolved in ethyl acetate, concentrated to an oil, and this procedure repeated twice with ethyl acetate, twice with dry ether, and twice with dry benzene to remove the acetic anhydride and pyridine. Then 75 ml of dry benzene was added, the solution heated to reflux and a small amount distilled to thoroughly dry the solution. This solution, after cooling to 0°, was treated with a solution of 9·93 ml of freshly distilled oxalyl chloride in 24·6 ml of benzene and stored at 25° for 3 hr. The mixture was then concentrated *in vacuo* to a colorless amorphous residue which was dissolved in 25 ml of dry benzene and reconcentrated.

A solution of this residue in 65 ml of dry benzene was added dropwise with stirring over a period of 10 min to about 170 ml of ethereal diazomethane cooled to −15°; the diazomethane was prepared from 8·85 ml of ethyl N-nitroso-N-methyl urethane. The yellow mixture was held at −15° for an additional 0·5 hr, then stored at 0° overnight. After standing at 25° for 1·5 hr, the solvents were removed *in vacuo*. The amorphous residue dissolved in 30 ml of dry ether and reconcentrated.

The pale yellow product in 103·5 ml of dry ether was treated with 24·1 ml of 1·368 N hydrogen chloride in ether and the mixture stored at 25° overnight. The initial evolution of nitrogen had ceased. The solution was poured onto 100 g of ice with stirring and the product extracted with 2 portions of ether. The combined extracts were washed free of acid with 3 portions of water, then washed once with saturated salt solution, filtered through magnesium sulfate and the ether removed *in vacuo* to give 2·71 g of amorphous residue which crystallized on adding ether. Recrystallization of a portion of this material from ether gave 21-*chloro*-17β-*methyl*-17-iso*pregnane*-11,20-*dione*-3α-*ol* 3-*acetate* as prism, m.p. (micro) (ca. 173°).

Anal. Calcd. for $C_{24}H_{35}O_4Cl$: Cl, 8·38. Found: Cl, 8·05.

A 2·50 g sample of the chloroketone above was dissolved in 27·5 ml of glacial acetic acid at 25°. The solution was swirled and 3·59 g of zinc dust added in portions over 15 min. The temperature of the mixture slowly rose to 33°, then dropped to 25°. After about one-quarter of the zinc had been added, the solution became bright yellow and then faded to nearly colorless. Finally the mixture was heated at 100° for

1 hr with occasional swirling, 150 ml of water was added and the product extracted with 3 portions of ether. The combined extracts were washed successively with water twice, with 5% aqueous sodium bicarbonate until neutral, again with water 3 times and finally with saturated salt solution. The washed extracts were filtered through magnesium sulfate and the solvent removed *in vacuo* to give a crystalline residue, weight 2·03 g. This was chromatographed over 152 g of acid-washed alumina. After development with 1:3 and 1:2 benzene–petroleum ether (b.p. 30–60°), crystalline material was eluted with 1:1 and 2:1 benzene–petroleum ether and with benzene. All these fractions melted in the range 160–173° and were combined, weight 1·805 g. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 1·39 g of the 17β-methyl-17-*iso*pregnane-11,20-dione-3α-ol 3-acetate (XVIII), m.p. (micro) 171–174°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74·23; H, 9·28. Found: C, 73·99; H, 9·38.

3α,17α-*Dihydroxy*-17β-*methyletiocholane*-11-*one* (XIX)

(a) *Via peroxytrifluoroacetic acid oxidation of* XVIII. A solution of peroxytrifluoroacetic acid was prepared as described above from 1·64 ml of 90% hydrogen peroxide and 10·16 ml of trifluoroacetic anhydride. This was added to a solution of 777·0 mg (2·0 mmoles) of 17β-methyl-17-*iso*pregnane-11,20-dione-3α-ol 3-acetate (XIX) in 30 ml of methylene chloride containing 26·0 g of disodium hydrogen phosphate; the addition required 20 min. The mixture was allowed to stand at 25° overnight, then heated under reflux for 1 hr. Addition of water and extraction as described above gave 0·79 g of amorphous residue. This was hydrolyzed by heating under reflux for 3 hr with 20 ml of methanol and 10 ml of 30% aqueous potassium hydroxide. Removal of the methanol *in vacuo*, dilution with water and extraction with ether gave 0·39 g of an amorphous mixture which was chromatographed over 19·5 g of neutral alumina. The fractions eluted with 10, 20 and 50% ether in benzene and with ether were combined, weight 231 mg. A portion of this oily material on acetylation with acetic anhydride and pyridine at 25° for 2 hr and recrystallization from petroleum ether (b.p. 30–60°) had the m.p. 164–170·5°, undepressed on admixture with the starting acetate (XVIII).

After further development of the column with 10, 25 and 50% acetone in ether, the fractions eluted with acetone were combined, weight 99·5 mg. Recrystallization from acetone–ether followed by recrystallization from ethyl acetate gave 26·0 mg of prisms, m.p. (micro) 196–199·5°, undepressed on admixture with a sample of 3α,17α-dihydroxy-17β-methyletiocholane-11-one prepared in part (b) below and showing identical infrared spectra.

(b) *Via the sequence originating from* 3α-*acetoxy*-17α,21-*dibromopregnane*-11-*one* (IV). A solution of 14·96 g of 3α-acetoxypregnane-11,20-dione in 290 cm^3 glacial acetic acid was brominated with 13 g of bromine at room temperature. After complete addition of bromine the reaction mixture was heated at 40–50° for 30 min and the product precipitated with water and filtered. The product was extracted with ethyl acetate (500–600 cm^3) and the ethyl acetate extract washed with dilute aqueous potassium bicarbonate solution. The solvent was concentrated *in vacuo* and the dibromide (IV) crystallized from acetone, wt. 16 g, m.p. 173–175° (reported ref. 8 m.p. 177°)

The above dibromide in 650 cm^3 of methanol refluxed 2 hr with 35 g of potassium

hydroxide in 35 cm³ of water. At the end of this period the methanol was removed *in vacuo* replaced with water and the aqueous solution extracted twice with ether. Acidification precipitated the crude acid III. The latter was dissolved in ethyl acetate, dried over magnesium sulfate and concentrated to the point of crystallization. There was obtained 8 g of the $\Delta^{\alpha,\beta}$-acid XXI recrystallized from acetone–hexane, m.p. 247°. λ_{max}^{Nj} 3 μ, 5·80 μ, 6·02 μ, 5·93 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72·83; H, 8·67. Found: C, 73·02; H, 8·65.

The $\Delta^{\alpha,\beta}$-acid XXI (3·5 g) in 15 cm³ of quinoline and 0·35 g of copper powder was heated under reflux for 1 hr. Evolution of carbon dioxide had ceased after 30 min. The reaction product was diluted with ether, filtered through Supercel, and the quinoline removed by extraction with dilute hydrochloric acid. Concentration of the ether produced 3·1 g of crystalline product which appeared to be homogeneous by alumina chromatography m.p. 145–146°. Recrystallization from ether–petroleum ether afforded the *exomethylene derivative* (XXII), m.p. 147–147·5°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79·39; H, 10·00. Found: C, 79·47; H, 9·93.

A solution of 1·5 g of the olefin XXII in 5 cm³ of benzene was treated with 26 cm³ of 0·21 M perbenzoic acid in benzene for 18 hr. At the end of this period the reaction mixture was washed free of acid with 5% aqueous sodium carbonate solution. Concentration produced 1·2 g of a crystalline product which did not melt sharply (135–150°) and was therefore processed without further purification.

The above epoxidized olefin (1 g) was dissolved in 60 cm³ of tetrahydrofuran and refluxed with 1 g of lithium aluminum hydride for 2 hr. The reduction product was acetylated with acetic anhydride in pyridine and the acetylated product oxidized in acetic acid with 300 mg of chromic acid. Chromatography of the oxidized product afforded oily fractions which were saponified to give crystalline 3α,17α-dihydroxy-17β-methyletiocholane-11-one (XIX) m.p. 195–197·5° $[\alpha]_D^{25°}$ +39·6° (1·0 acetone).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 75·00; H, 10·00. Found: C, 74·96; H, 10·00.

This material was found to be identical in mixed m.p. and infrared comparison with XIX obtained above in part (a).

3α-*Acetoxy*-21-*methanesulfonyloxypregnane*-11,20-*dione* (XXIVa)

A solution of 2 g of 3α-acetoxy-21-hydroxypregnane-11,20-dione[18] (XXIV) in 9 cm³ of pyridine was treated with 3 cm³ of methanesulfonyl chloride at 0–5° for 18 hr. The reaction mixture was decomposed with ice-water extracted with ether and the ether solution washed with dilute aqueous hydrochloric acid, potassium bicarbonate solution and finally dried and concentrated. The residue was crystallized from acetone ether m.p. 164·5–166°.

Anal. Calcd. for $C_{24}H_{36}O_7S$: C, 61·54; H, 7·69. Found: C, 61·85; H, 7·94.

3α-*Acetoxy*-21-*bromopregnane*-11,20-*dione* (XXV)

A solution of 2 g of the 21-mesylate derivative XXIVa in 10 cm³ of acetone was refluxed for 2 hr with 4 g of lithium bromide. The product crystallized as needles from ether, m.p. 164–165·5°.

Anal. Calcd. for $C_{23}H_{33}O_4Br$: C, 60·93; H, 7·28; Br. 17·66. Found: C, 61·18; H, 7·26; Br, 17·59.

[18] Huang-Minlon and R. Pettebone, Unpublished work.

Rearrangement of carbinols XVII and XIX

Samples of XVII and XIX (100 mg) were heated in 10 cm³ of formic acid on a steam bath for 2 hr according to the method of Kägi and Miescher.[15] The product was identical in both instances giving XX as prisms from ligroin, m.p. 129–131·5°. $\lambda_{max}^{CH_2OH}$ 240 mμ ε = 17,200 λ_{max} 5·79 (OAc), 6·00 (conj. C=O).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76·78; N, 9·31. Found: C, 76·52; H, 9·58.

Acknowledgement—The authors are indebted to H. L. Slates for the preparation of a comparison sample of 3α-acetoxy-17β-hydroxy-17-*iso*pregnane-11-one.

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THE CHEMISTRY OF SANTONIN—V*

SOME REDUCTION PRODUCTS OF 11β(H)-SANTONIN

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Abstract—Three tetrahydro-11β(H)-santonins have been obtained by the hydrogenation of 11β(H)-santonin over palladised charcoal. Two of these tetrahydro-11β(H)-santonins were previously obtained by Clemo. They have now been shown to have a *trans*-A/B ring-fusion, by relating them to the stable *trans*-A/B ring-fused tetrahydrosantonin. A third tetrahydro-11β(H)-santonin (*cis*-A/B ring-fusion) and 1:2-dihydro-11β(H)-santonin have been isolated in small quantities from the same reaction. A 4:5-dihydro-11β(H)-santonin has been isolated from the hydrogenation of potassium 11β(H)-santoninate in methanol over a platinum catalyst. The preparation of two hexahydro-11β(H)-santonins is described.

THE stereochemistry of the reduction products of santonin (I) has been the subject of several recent investigations.[1,2,3,4,5] Though the Japanese authors originally gave the opposite assignment,[1] it is now agreed[2,3,4] that the so called α-tetrahydrosantonin† has a *trans*-A/B ring-fusion while β-tetrahydrosantonin has a *cis*-A/B ring-fusion.

This result is of interest, since the main product of the hydrogenation of santonin thus has the *trans*-A/B ring-fusion. In the steroid 4-en-3-ones hydrogenation gives varying results. For example, cholestenone yields predominantly the *cis*-fused coprostanone,[7,8] whilst testosterone affords the *trans*-fused androstane-17β-ol-3-one. Amongst simpler compounds one finds that 4:10-dimethyloctal-4-en-3-one is hydrogenated over palladised charcoal to *trans*-4:10-dimethyldecal-3-one.[2] It might be argued that differences in stereochemical reduction of these systems can be traced to the nature of attached groups, in that these might inhibit the absorption of either the α- or β-face of the ring system on the catalyst.

It seemed to us worth while to study the hydrogenation of 11β(H)-santonin, which differs from santonin only in the configuration at C_{11}. In santonin, the 11β-methyl group should favour absorption of the α-face of the molecule on the catalyst, and hence products having a *trans*-A/B ring-fusion should be formed.

In 11β(H)-santonin (II), the 11α-methyl group might be expected to discourage

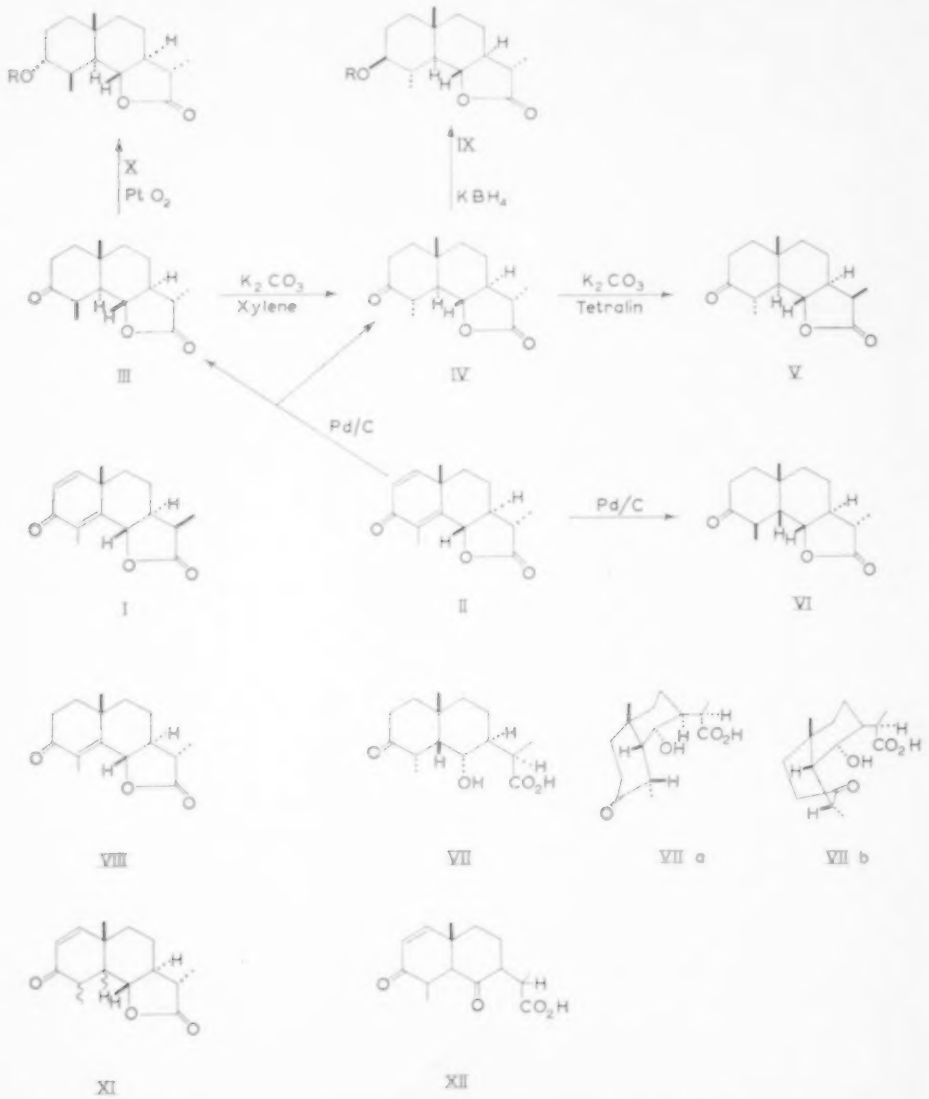
* Part IV. W. Cocker, K. Crowley, J. T. Edward, T. B. H. McMurry and E. R. Stuart, *J. Chem. Soc.* 3416, (1957).

† The prefixes α and β are used in this context in the manner employed by the earlier workers in this field.[6] Elsewhere we use the nomenclature of Cocker and McMurry[3].

[1] M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955); A. Tahara, *J. Org. Chem.* **21**, 442 (1956).
[2] M. Yanagita and R. Futaki, *J. Org. Chem.* **21**, 949 (1956); M. Yanagita and H. Ogura, *J. Org. Chem.* **22**, 1092 (1957).
[3] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956).
[4] B. Riniker, Thesis, E. T. H., Zurich (1955); C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).
[5] Ö. Kovács, V. Herout, M. Horák and F. Šorm, *Chem. Listy*, **49**, 1856 (1955); *Coll. Czech. Chem. Commun.* **21**, 225 (1956).
[6] Cf. Sir John Simonsen and D. H. R. Barton, *The Terpenes* (Vol. III) p. 292. Cambridge University Press (1952).
[7] H. Grasshof, *Z. Physiol. Chem.* **223**, 249 (1934).
[8] A. Butenandt, K. Tscherning and G. Hanisch, *Ber. Dtsch. Chem. Ges*, **68**, 2097 (1935).

absorption on the α-face, and lead to the formation of greater amounts of products with *cis*-A/B ring-fusion.

Accordingly, we have investigated the hydrogenation of 11β(H)-santonin under various conditions, and we have found that the configuration at C_{11} has little influence on the manner of reduction.



Clemo[9] showed that reduction of 11β(H)-santonin with hydrogen afforded a mixture of two tetrahydro compounds, m.p. 125–126° and 207–208°, which on reduction by the Clemmensen method gave the same deoxytetrahydro-11β(H)-santonin.

[9] G. R. Clemo, *J. Chem. Soc.* 1343 (1934).

This result implied that the two compounds had the same type of ring-fusion and hence could only differ in configuration at C_4, the less stable isomer being epimerised at this centre under the strongly acid conditions of the reaction (cf. Kováks *et al.*[5]).

We have hydrogenated 11β(H)-santonin in acetic acid and have obtained the two tetrahydro compounds described by Clemo in a total yield of 75 per cent. From the products of the same reduction we have also isolated a third tetrahydro compound, m.p. 140·5–141·5°, which like the other two is dextrorotatory. In addition a dihydro-11β(H)-santonin was also isolated.

The isomer, m.p. 207–208°, proved to be less stable at C_4 than the compound, m.p. 125–126°, for the former was readily converted into the latter either (*a*) by treatment, in the cold, with a solution of toluene-*p*-sulphonic acid in acetic acid,[5] or (*b*) with potassium carbonate in boiling xylene.[10] The lower-melting compound thus has an equatorial methyl group at C_4 (cf. Cocker and McMurry[3] and Kováks *et al.*[5]). The nature of the A/B ring junction was demonstrated by epimerisation of the lower-melting compound at C_{11}, thus affording 3-oxo-5:11α(H),4:6β(H)-eudesman-6:13-olide (α-tetrahydrosantonin) (V), whose A/B ring junction is known to be *trans* fused.[1,2,3,4,5,6] Hence we can now state that the higher- and lower-melting tetrahydro-11β(H)-santonins, first prepared by Clemo,[9] are, respectively, 3-oxo-4:5α(H), 6:11β(H)-eudesman-6:13-olide (III) and 3-oxo-5α(H)4:6:11β(H)-eudesman-6:13-olide (IV). It is interesting to note that in order to isomerise (IV) to (V) we had to employ potassium carbonate in boiling tetrahydronaphthalene, whereas the isomerisation of 11β(H)-santonin to santonin can be effected with potassium carbonate in boiling xylene.[10]

The third, and new, tetrahydro-11β(H)-santonin (m.p. 140·5–141·5°) that we now describe must obviously have *cis*-A/B ring-fusion, and, since it is stable to potassium carbonate in boiling xylene, we conclude that it has an equatorial methyl group at C_4, and this must have the β-configuration. The new tetrahydro compound is thus 3-oxo-4α(H),5:6:11β(H)-eudesman-6:13-olide (VI).

In an earlier paper in this series,[3] we pointed out that in the corresponding santonin series, the *cis*-A/B ring-fused tetrahydrosantonin (β-tetrahydrosantonin[6]) and the derived hydroxy acid have opposite configurations at C_4. Lactonisation of the hydroxy acid performed by heating at 200° effects epimerisation at C_4, a configurational change that can be reversed when the lactone is hydrolysed. We assigned the α (axial) configuration to the 4-methyl group in the lactone and β (equatorial) in the acid. These assignments were based upon the following facts. Reduction of the tetrahydrosantonin over Adams's catalyst gave a hexahydro compound, also derived in low yield by hydrogenation of santonin itself. Since the major product of the latter reaction was a hexahydrosantonin (*trans*-A/B fused system) having *cis* arrangement of hydrogen atoms at C_4 and C_5, it was considered likely that the minor product of reduction (*cis*-A/B fused system) would also have *cis* arrangement of hydrogen atoms at C_4 and C_5. That is, these hydrogen atoms would have β configuration, resulting in an axial 4α-methyl group. However, this argument is not valid. It has been shown that the *cis*-A/B fused tetrahydrosantonin has a rotatory dispersion curve similar to that of a 3-oxo-5β-steroid, implying that the 4-methyl group is β (equatorial)[1]. The 4-methyl group in the tetrahydrosantoninic acid (VII) must consequently be α-orientated.

[10] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4430 (1955).

The stability of C_4 with its α-orientated methyl group in the hydroxy acid can be explained if it is assumed that it does not have the normal chair conformation of ring A as in (VIIA), but rather a boat conformation as in (VIIB) in which the 4-methyl group becomes equatorial.* The latter structure will be stabilised by hydrogen bonding between the 6-hydroxyl and the 3-oxo groups.

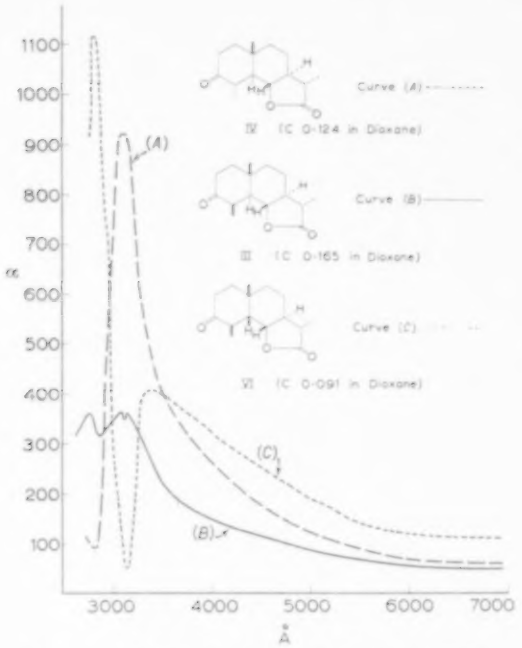


FIG. 1. Rotary dispersion of tetrahydro-11β(H)-santonins

That the assignment of structure to compounds (III), (IV) and (VI) is correct is shown by inspection of their rotatory dispersion curves, which were made available to us through the kindness of Professor Djerassi. Fig. 1 shows that the tetrahydro-11β(H)-santonin, m.p. 125–126° (IV) (curve A) has a typical *trans*-A/B fused 3-oxo-5α-steroid rotatory dispersion curve, which is similar to that of 3-oxo-5:11α(H)4:6β(H)-eudesman-6:13-olide (V).[4,6] Similarly the dispersion curves of the tetrahydro

* While this paper was in course of preparation, Banerji *et al.*[11] propounded a similar view. We first mentioned our view to Professor Djerassi early in 1957, after he had pointed out to us that the rotatory dispersion curve of the *cis*-tetrahydrosantoninic acid mentioned above was like that of a *trans*-fused 3-oxo-5β-steroid.

[11] J. C. Banerji, D. H. R. Barton and R. C. Cookson, *J. Chem. Soc*, 5041 (1957).

compounds, m.p. 207–208° (III), and 140–141·5° (VI) (curves B and C, respectively) are closely similar to those of 3-oxo-4:5:11α(H),6β(H)-eudesman-6:13-olide and 3-oxo-4:11α(H),5:6β(H)-eudesman-6:13-olide, respectively.[3,4]

It is also interesting to compare the molecular rotations of the corresponding tetrahydrosantonins and 11β(H)-santonins and these are set out in Table 1.

It is obvious from Table 1 that the two sets of compounds show similar trends in molecular-rotation changes, thus implying similar stereochemical relationships.

TABLE 1. MOLECULAR ROTATIONS OF TETRAHYDROSANTONINS AND TETRAHYDRO-11β(H)-SANTONINS

Santonin	$[M]^D$	Santonin	$[M]^D$
3-Oxo-5:11α(H),4:6β(H)-eudesman-6:13-olide (V)	+ 70°	3-Oxo-5α(H),4:6:11β(H)-eudesman-6:13-olide (IV)	+ 205°
3-Oxo-4:5:11α(H),6β(H)-eudesman-6:13-olide	+ 179°	3-Oxo-4:5α(H),6:11β(H)-eudesman-6:13-olide (III)	+ 295°
3-Oxo-4:11α(H),5:6β(H)-eudesman-6:13-olide	+ 25°	3-Oxo-4α(H),5:6:11β(H)-eudesman-6:13-olide (VI)	+ 166°

The dihydro-11β(H)-santonin mentioned above proved to be the 1:2 dihydro compound (VIII). This structure is assigned, since in the ultra-violet region it shows a maximum at 2470 Å (log ε 4·18); this is close to the expected value[12] of 2520 Å. A second peak at 3150 Å (log ε 1·8), and peaks at 1780 (lactone), 1670 (keto), 1615 (C=C) and 1430 cm^{-1} (CH_2 next to C=O in a 6-membered ring) in the infra-red region support the αβ-unsaturated ketone structure. The ketone also forms a 2:4-dinitrophenylhydrazone, which shows typical maximum absorption at 3850 Å (log ε 4·56).

The dihydro compound was obtained in greater yield by hydrogenation of 11β(H)-santonin in ethanol over an activated Raney nickel catalyst[13] at room temperature and pressure.

When 3-oxo-5α(H),4:6:11β(H)-eudesman-6:13-olide (IV) was reduced with potassium borohydride, 3β-hydroxy-5α(H),4:6:11β(H)-eudesman-6:13-olide (IX, R = H) was obtained in good yield. Reaction with acetic anhydride and pyridine gave the corresponding acetate with *positive* increment in molecular rotation (Table 2), and hence[14,15,16,17] the hydroxyl and its acetate must be β (equatorial) orientated, a result to be expected of the method of preparation of the alcohol.

When 11β(H)-santonin was reduced in acetic acid over Adams's catalyst, it afforded 3α-hydroxy-4:5α(H),6:11β(H)-eudesman-6:13-olide (X, R = H). The orientation of the hydroxyl follows from the *negative* increment in molecular rotation (Table 2) on acetylation. From the method of preparation it may be inferred that

[12] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene* (3rd ed.) p. 190. Reinhold, New York (1949).
[13] A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.* **68**, 1471, (1946).
[14] W. Klyne and W. M. Stokes, *J. Chem. Soc.* 1979 (1954).
[15] W. M. Stokes and W. Bergmann, *J. Org. Chem.* **17**, 1194 (1952).
[16] J. A. Mills, *Chem. & Ind.* 218 (1953).
[17] D. H. R. Barton and A. Nickon, *J. Chem. Soc.* 4665 (1954).

the hydroxyl is axial, and this is confirmed by the fact that the alcohol is obtained when the *trans*-fused tetrahydro-11β(H)-santonin (III) is reduced over platinic oxide in acetic acid.

Reduction of potassium 11β(H)-santoninate in methanol over Adams's catalyst affords the *cis*-fused tetrahydro compound (VI), a result to be expected by analogy with the santonin series.[3] At the same time the hexahydro compound (X) was obtained and a 4:5-dihydro compound 3-oxo-4:5ξ(H),6:11β(H)-eudesm-1-en-6:13-olide (XI).

TABLE 2. MOLECULAR ROTATIONS OF HEXAHYDRO-11β(H)-SANTONINS AND ACETATES

Santonin	$[M]_D$ of alcohol	$[M]_D$ of acetate	Δ_1*
3β-Hydroxy-5α(H),4:6:11β(H)-eudesman-6:13-olide (IX, R = H)	+302°	+315°	+13°
3α-Hydroxy-4:5α(H),6:11β(H)-eudesman-6:13-olide (X, R = H)	+237°	+164°	−73°

* Δ_1 is defined as suggested by Klyne and Stokes.[14]

The double bond is located in the 1:2-position, since the substance shows maxima at 2280 Å (log ε 3·89) and 3180 Å (log ε 1·51), in close agreement with the spectrum of 3:6-dioxoeudesm-1-en-13-oic acid (XII).[2,12]

The formation of (X) in small yield in the reduction of potassium 11β(H)-santoninate is probably due to the presence of some unhydrolysed santonin in the methanolic solution of the salt.

EXPERIMENTAL

Ultra-violet spectra were (unless otherwise stated) measured for ethanolic solutions with a Beckman DU instrument. Infra-red spectra were measured in chloroform solutions with a Hilger 800 double-beam instrument. $[\alpha]_D$ refer to chloroform solutions.

Hydrogenation of 11β(H)-*santonin* (cf. Clemo[9])

A mixture of 11β(H)-santonin (12 g), 10% palladised charcoal (2 g) and acetic acid (100 ml) was stirred in an atmosphere of hydrogen for 24 hr. Filtration and removal of solvent gave a solid, which was fractionally crystallised from ethyl acetate to give 3-oxo-4:5α(H),6:11β(H)-eudesman-6:13-olide (III) as rhombs (3·9 g), m.p. 206–208°, $[\alpha]_D^{15}$ +118·1° (*c*, 0·9) [max. at 1780 (lactone), 1710 cm^{-1} (ketone)] (Found: C, 72·1; H, 8·8. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9 per cent).

Removal of the mother-liquors from the crystallisation of (III), and two further crystallisations of the residue from ethanol, gave 3-oxo-5α(H),4:6:11β(H)-eudesman-6:13-olide (IV) (5·2 g), m.p. 125–126°, $[\alpha]_D^{15}$ +81·9° (*c*, 1·33) (max. at 1780, 1714 cm^{-1}) (Found: C, 71·6; H, 9·1. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9 per cent).

Concentration of the ethanolic mother-liquors from (IV) gave a solid (0·6 g), which on further recrystallisation from ethanol gave 3-*oxo*-4α(H),5:6:11β(H)-*eudesman*-6:13-*olide* (VI) as rhombs, m.p. 140·5–141·5°, $[\alpha]_D^{15}$ +66·6° (*c*, 1·75) (max. at 1784, 1720 cm^{-1}) (Found: C, 71·9; H, 9·0. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9 per cent).

In a second hydrogenation the above-mentioned mother-liquors deposited a

mixture of rhombs and hexagonal plates. The latter, separated by hand picking, were recrystallised from ethanol to give 3-*oxo*-6:11β(H)-*eudesm*-4*en*-6:13-*olide* (VIII), m.p. 121°, $[\alpha]_D^{15}$ + 112·5° (*c*, 1·2) [λ_{max} 2470 Å (log ε 4·18), 3150 Å (log ε 1·80); 1780 (lactone), 1670 (keto), 1630 cm^{-1} (C=C)] (Found: C, 72·6; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1 per cent). The 2:4-*dinitrophenylhydrazone* was obtained as orange-red plates from ethanol, m.p. 240° [λ_{max} 2610 Å, (log ε 4·04), 3850 Å (log ε 4·56)] (Found: C, 58·0; H, 5·5. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6 per cent).

Conversion of 3-*oxo*-4:5α(H),6:11β(H)-*eudesman*-6:13-*olide* (III) *to* 3-*oxo*-5α(H),-4:6:11β(H)-*eudesman*-6:13-*olide* (IV)

Method (a). The keto-lactone (III) (0·92 g), freshly ignited potassium carbonate (1 g) and dry xylene (50 ml) were heated under reflux for 30 hr. Filtration and removal of the solvent from the filtrate gave crude 3-oxo-5α(H),4:6:11β(H)-eudesman-6:13-olide (IV), which on crystallisation from ethanol was obtained (0·78 g), m.p. 124–125° undepressed on admixture with an authentic specimen.

Method (b). A mixture of the keto-lactone (III) (1·0 g), toluene-*p*-sulphonic acid (0·9 g) and acetic acid (10 ml) was set aside for 16 hr. Dilution with water and crystallisation of the product from ethanol gave the ketone (IV) (1·0 g), m.p. 125–126°.

Conversion of 3-*oxo*-5α(H),4:6:11β(H)-*eudesman*-6:13-*olide* (IV) *into* 3-*oxo*-5:11α(H),-4:6β(H)-*eudesman*-6:13-*olide* (V)

Method (a). A mixture of the ketone (IV) (1 g), anhydrous potassium carbonate (1 g) and dry tetrahydronaphthalene (50 ml) was heated under reflux for 4 hr. Filtration and removal of the tetrahydronaphthalene from the filtrate gave a product, which, after being washed with light petroleum and crystallised from ethyl acetate–light petroleum (boiling range 60–80°), gave 3-oxo-5:11α(H),4:6β(H)-eudesman-6:13-olide (0·3 g) as needles, m.p. 155°, undepressed by admixture with an authentic specimen.[3]

Method (b). The desired epimerisation also took place, but in small yield when the ketone (IV) (0·3 g) was heated under reflux for 4 hr with sodium methoxide, from sodium (2 g) in methanol (30 ml). Removal of methanol, dilution of the residue with water, acidification and extraction with ether gave an oil, which became partly solid on trituration with light petroleum. Chromatography in benzene–ether mixture (4 + 1) on Woelm brand acid alumina afforded a solid product, m.p. 116–140°. Crystallisation from ethyl acetate–light petroleum gave 3-oxo-5:11α(H),4:6β(H)-eudesman-6:13-olide (10 mg), m.p. and mixed m.p. 155°.

3-*Oxo*-6:11β(H)-*eudesm*-4-*en*-6:13-*olide* (VIII)

11β(H)-Santonin (3 g) was hydrogenated for 50 min in ethanol (250 ml) at room temperature and pressure in presence of Raney nickel (W_5) (1 g).[13] Filtration and removal of the solvent afforded crude 3-oxo-6:11β(H)-eudesm-4-en-6:13-olide (VIII), which crystallised (1 g) from ethyl acetate, m.p. 122–123°, identical with the material described above.

Reduction of 3-*oxo*-5α(H),4:6:11β(H)-*eudesman*-6:13-*olide* (IV)

3β-*Hydroxy*-5α(H),4:6:11β(H)-*eudesman*-6:13-*olide* (IX, R = H). The ketone (IV) (2 g) in methanol (30 ml) was mixed with potassium borohydride (0·12 g) in water (5 ml) and set aside for 1 hr. The solution was diluted with water and acidified, when it yielded a solid product (2 g), which on crystallisation from aqueous ethanol

gave 3β-*hydroxy*-5α(H),4:6:11β(H)-*eudesman*-6:13-*olide* (IX, R = H) as needles, m.p. 154°, $[\alpha]_D^{15}$ + 119·8° (*c*, 1·1) (Found: C, 71·35; H, 9·8. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6 per cent). Its *acetate* (IX, R = Ac) was obtained (0·15 g) when the alcohol (0·2 g) was heated on the water bath for 2 hr with a mixture of acetic anhydride (5 ml) and pyridine (5 ml). The acetate crystallised from aqueous ethanol as plates, m.p. 99–100°, $[\alpha]_D^{15}$ + 107·2° (*c*, 0·44) [max. at 1777 cm^{-1} (lactone); 1740, 1263 cm^{-1} (acetate)] (Found: C, 69·7; H, 8·8. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9 per cent).

Hydrogenation of 11β(H)-*santonin over platinic oxide*

3α-*Hydroxy*-4:5α(H),6:11β(H)-*eudesman*-6:13-*olide* (X, R = H). 11β(H)-Santonin (2 g) in glacial acetic acid (150 ml) was hydrogenated at room temperature and pressure over Adams's catalyst (0·1 g) until there was no further uptake of hydrogen. Filtration and removal of solvent gave a solid product, which after two recrystallisations from ethyl acetate–light petroleum gave 3α-*hydroxy*-4:5α(H),6:11β(H)-*eudesman*-6:13-*olide* (X, R = H) as needles (0·6 g), m.p. 146–147°, $[\alpha]_D^{15}$ + 94° (*c*, 0·99) (Found: C, 71·6; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6 per cent). Acetylation of the alcohol with acetic anhydride and pyridine afforded its *acetate* (X, R = Ac), which crystallised from ethyl acetate, m.p. 170–172°, $[\alpha]_D^{15}$ + 55·7° (*c*, 1·1) [max. at 1774 cm^{-1} (lactone); 1727, 1264 cm^{-1} (acetate)] (Found: C, 69·3; H, 8·5. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9 per cent).

Reduction of 3-*oxo*-4:5α(H),6:11β(H)-*eudesman*-6:13-*olide* (III). Hydrogenation of (III) (0·37 g) in acetic acid (100 ml) over platinic oxide (0·11 g) gave an oil, which on acetylation with acetic anhydride and pyridine gave the acetate (X, R = Ac) (0·32 g), m.p. and mixed m.p. 170–172°.

Hydrogenation of potassium 11β(H)-*santoninate*. 11β(H)-Santonin (10 g) was heated under reflux for 20 min in methanol (200 ml) containing potassium hydroxide (4 g), cooled and hydrogenated at room temperature and pressure over Adams's catalyst (0·32 g). After 18 hr the mixture was filtered, concentrated to 30 ml, acidified with dilute hydrochloric acid and then heated under reflux for 1 hr to effect lactonisation. Removal of solvents gave an oil, which on standing in ether gradually deposited crystals (0·85 g). Crystallisation from aqueous ethanol and then from ethyl acetate gave pure 3-oxo-4α(H),5:6:11β(H)-eudesman-6:13-olide (VI), m.p. and mixed m.p. 140°.

Evaporation of the ethereal mother-liquors gave an oil (8·3 g), which was repeatedly extracted with boiling light petroleum (boiling range 60–80°). The early extracts gave in all about 1 g of (VI), m.p. 138–139°. Later extracts deposited a solid (0·32 g), which after crystallisation from ethyl acetate had m.p. 147–148°, identical with (X).

In a similar experiment, but when previously used platinum black (0·3 g) (from Adams's catalyst) was employed, the ether solution mentioned above deposited crystals (0·7 g). Crystallisation first from ethyl acetate after treatment with charcoal and then twice from ethanol gave 3-*oxo*-4:5ξ(H),6:11β(H)-*eudesm*-1-*en*-6:13-*olide* (XI) as needles, m.p. 207–208°, $[\alpha]_D^{15}$ −20·7° (*c*, 0·8) [max. at 2280 Å (log ε 3·89), 3180 Å (log ε1·51); 1778 cm^{-1} (lactone), 1685 cm^{-1} (ketone)] (Found: C, 72·1; H, 8·2. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1 per cent.

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SOME ASPECTS OF THE CHEMISTRY OF CIGARETTE SMOKE—I

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Abstract—Eight varieties of cigarettes have been "smoked", the smoke contents dissolved in methyl alcohol and separated into volatile in methyl alcohol, neutral, acidic, phenolic and basic fractions. The water soluble part of the dissolved mixture from seven of the varieties is acidic and basic from the eighth variety.

The acidic and phenolic fractions have been examined in some detail and their possible effect on health comented on.

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IN the course of a detailed study of the chemistry of cigarette smoke during recent years, numerous statistics have appeared, particularly in the United States of America and the United Kingdom, pointing to a definite connection between lung cancer and cigarette smoking in those countries. Thus the figures for the crude death rate from lung cancer per million in thirteen different countries for 1950–1951 show[1] such a wide variation that they raise the question as to whether there is any marked difference in the nature of the smoke from the cigarettes commonly used in different countries. There is no suggestion that cigar smoke, which is alkaline, is a causative agent, whereas cigarette smoke is usually strongly acidic. Pipe tobacco smoke is also stated to be acidic. The thirteen countries referred to above do not include any from behind the "curtain," but it was stated by Dr. Savittski at the Cancer Conference in Brazil in 1954 that there is no relation between tobacco and lung cancer in Russia and a like claim has been made for Poland.

After trying to obtain Russian cigarettes of the tubed "Dyeli" variety for over 2 years, a few hundred were obtained in Rumania recently, thanks to help from the Rumanian Academy, and what follows deals mainly with a comparison of the smoke from these and from seven brands from other countries, including an English variety on which the great majority of my work has been done. Although only 350 "Dyeli" have been smoked in three experiments (Example 4, Table 1), consistent results were obtained. All experiments have been done under standard conditions, but varying atmospheric conditions during smoking have some effect on the results. Further, in view of the smaller number of cigarettes smoked in Examples 2, 3, 5, 6, 7 and 8, the figures after the decimal point (except for the pH) may be rather less reliable.

In order to make the results as comparable as possible, they are based on 100 g of tobacco smoked rather than on the number of cigarettes, which vary considerably in weight.

The striking fact that emerges, however, is the pH of 8·9 for the "Dyeli," whereas all the other seven values are markedly acidic. This type with 3 cm of tobacco at the front and a 5 cm empty tube at the mouth end is much the most difficult to light and its 3 cm of tobacco takes as long to burn as the 7 to 8 cm of tobacco in the other varieties. Contrary to a common notion, the tubes condense very little of the smoke products (only 6 mg approximately per tube), but they probably cool the smoke appreciably before it enters the mouth. Incidentally the filter tips of a popular

[1] R. Doll, *Advances in Cancer Research* (Vol. III).

TABLE 1. PRODUCTS IN SMOKE FROM 100 g OF TOBACCO

Example No.	Tobacco tested	Crude hentriacontane (g)	Volatile in MeOH (g)	*M* (g)	Soluble in water		Soluble in NaOH solution (g)	Soluble in AcOH and HCl (g)	Esters (g)	M_N (g)
					Amount (g)	pH				
1.	English	0·23	0·35	6·8	2·7	4·2	2·1*	0·14	0·39	1·34
2.	U.S. (Chesterfield)	0·23	0·76	9·65	3·5	4·8	2·8	0·45	0·3	2·47
3.	U.S. (Camel)	0·36	1·08	8·95	3·1	5·2	2·4	0·5	0·54	2·27
4.	Russian (Dyeli)	0·26	0·8	8·75	3·2	8·9	2·8†	0·43	0·58	1·7
5.	Rumanian Marasesti	0·16	0·54	6·86	2·1	5·1	2·3	0·48	0·23	1·63
6.	French (Gitane)	0·2	0·88	8·75	2·98	5·7	2·32	0·77	0·77	1·9
7.	German (Peer)	0·16	1	9·2	3·7	4·9	2·77	0·15	0·77	1·74
8.	Black Russian (Sobranie)	0·24	(Lost)	9·6	3·5	4·9	3	0·33	0·74	1·95
9.	English (MeOH extracted)	0·05	Trace?	7	3·97	5·5	2·24	0·17	0·27	0·35

* 0·22 g phenolic. † 0·26 g phenolic.

English brand are a convenient source of at least one crystalline compound that can only be isolated from M_N (Table 1) with difficulty.

The pH of 8·9 (Example 4) is due to the presence of nicotine and the non-production of any quantity of water-soluble acids, although as can be seen from Table 1 the Dyeli smoke has almost the highest proportion of sodium hydroxide soluble "free acids" (including phenols) of any of the eight varieties. The presence of the nicotine is proved by distillation under reduced pressure, when, on the addition of picric acid to the distillate, only pure nicotine dipicrate separates almost at once.

The cigarettes in Example 8 are stated to be made in the United Kingdom from Russian tobacco.

Although most of my work has been done on the final neutral M_N fraction from Example 1 and some crystalline products isolated and analysed, it is to the acidic and phenolic constituents in Example 1 that my further remarks will be mainly directed.

It may be said, however, that, although M_N is predominately hydrocarbon in character, it contains very small amounts of aromatic hydrocarbons, but appreciable amounts of nitrogenous material (even after treatment with potassium) and oxygen-containing compounds, some of which have been obtained crystalline and analysed but not yet identified.

It is now generally agreed that the 3:4-benzopyrene content of M_N cannot account for the effect claimed for cigarette smoke. Thus none has been isolated therefrom

and its presence to the extent of about 1 p.p.m. is based on spectrographic evidence, which is usually qualified by benzopyrene *or* an alkyl derivative.

This being so, the question arises as to what other factor or factors might separately or together be responsible for the lung cancers claimed to be due to the cigarette smoke. It seems that two such factors are present that could produce the result and they will be referred to at the end of this paper.

EXPERIMENTAL

Method of smoking and the isolation of the products

All carbon–hydrogen analyses and molecular-weight determinations are by Drs. Weiler and Strauss at Oxford.

The cigarettes have been "smoked" twelve at a time in an apparatus designed to simulate average natural smoking. After a variety of solvents for the absorption of the products had been tried in an effective five-fold absorbing system, methanol was found to be both effective and convenient. It has been used for all the work to be described.

The resulting methanolic solutions in all the eight examples deposited a greasy solid. (Only in the case of Example 4 did this lead to trouble during the experiments, through frequent choking at a constriction in the apparatus.) This grease distils (vacuum) and several crystallisations from benzene–ethanol raises the m.p. of the waxy plates to 69° (Found: C, 85·1; H, 14·5; mol. wt., 332. Calc. for $C_{31}H_{64}$: C, 85·3; H, 14·7 per cent; mol. wt., 436). Although the found molecular weight differs appreciably from the calculated value, there is little doubt that the purified material is hentriacontane. Wright and Wynder[2] claim that 90 per cent of the crude mixture is this hydrocarbon, but no mass-spectrometric study of it appears to have been made (see also Kosak *et al.*[3]). Further, hentriacontane has been shown to be present in natural tobacco leaf and Example 9 shows that little of it is formed by burning extracted tobacco.

Evaporation of the methanolic solution to dryness on the water bath (finally under reduced pressure) gives a syrup *M* (Table 1) and a yellow rather choking distillate due to volatile products. Some of these have been isolated, purified and analysed and appear (apart from a trace of phenols) to be mainly terpenoid in character. So far, only dipentene has been identified from the mixture of at least eleven compounds (Found: C, 87·6; H, 12·1. Calc. for $C_{10}H_{16}$: C, 88·2; H, 11·8 per cent). Its tetrabromide melts at 124–125° alone or mixed with authentic dipentene tetrabromide.

Separation of mixture M

Mixture *M* has been shaken with a mixture of water and benzene (twice), when a trace of an acidic tar is left, which is easily soluble in ethanol. The pH values (Table 1, column 7) refer to the aqueous solutions so obtained. The acids in this solution will include fatty ones simpler than caproic, which is only very slightly soluble in water, and other easily soluble types such as oxalic acid. If this solution, which contains 40 per cent of *M*, is distilled under reduced pressure, the distillate has a pH of 4·7 and readily reduces silver nitrate, thus indicating the presence of

[2] G. Wright and E. L. Wynder, *Proc. Amer. Ass. Cancer Res.* **2**, 159 (1956).
[3] Kosak *et al.*, *J. Nat. Cancer Inst.* **17**, 3375 (1956).

formic acid. A number of acids have been claimed to be present in tobacco smoke by earlier workers, and Kosak[4] states that formic, acetic, butyric, valeric and caproic acids are in the smoke from the destructive distillation of tobacco, whilst others such as succinic and citric might be present. The conditions in a burning cigarette would probably yield a very different mixture. In harvested tobacco leaf malic and citric acids amount to from 9 to 14 per cent of the weight of the dried leaves and oxalic to 2·5 per cent.

The mixture in the above-mentioned benzene solution (approximately 60 per cent of *M*) was shaken twice in ethereal solution with 4% sodium hydroxide. (If the

TABLE 2. COMPOSITION OF FRACTIONS

A—methyl esters, b.p. 83–150°/2 mm from the A_2 fraction of "free" acids
B—methyl esters undistilled from the A_2 fraction of "free" acids
C—methyl esters undistilled from the A_3 fraction
D—methyl esters undistilled from the acids soluble in light petroleum after hydrolysis (see p. 172).

	A (per cent)	*B* (per cent)	*C* (per cent)	*D* (per cent)
Eluted before C_{14}—contains 2 per cent of lauric*	32		10	13
C_{14} Myristic	4			1
C_{14} to C_{16}, X_1, X_2, X_3†	3·5			1·5
C_{16} Palmitic	32		4	26·5
C_{16} Palmitoleic	1·5			1·0
C_{16} to C_{18}, X_4, X_5‡	2	Same		1
C_{18} Stearic	4	acids		1·5
C_{18} Oleic	7			9·0
C_{18} Linoleic and linolenic	13		2·5	33
C_{20} Arachidic	0·5			0·5
C_{20} X_6—unsaturated	0·5			
C_{26} Cerotic	0			
Non-volatile	0	12	83·5	15
	100	100	100	100

* The 30 per cent contains about 15 per cent of saturated and 15 per cent of unsaturated acids, of which 20 per cent are straight chain and 10 per cent branched or cyclic. There are at least fifteen and probably more compounds present.

† X_1, X_2 and X_3 are neither branched nor cyclic; one is unsaturated.

‡ X_4 and X_5 are saturated. Neither is highly branched nor cyclic. One appears to be C_{17} and the other an isomer of C_{18}.

dark alkaline solution is allowed to stand, a small amount of a sodium salt separates, from which a crystalline acid can be isolated.)

Acidification of the dark alkaline solution of the *free* acids and phenols in the smoke and ether extraction left 0·36 g of dark solid acids (A_1), insoluble in benzene also, but easily soluble in ethanol. These acids are complex non-fatty acids and probably more highly oxygenated compounds. The "acids" recovered from the ether (1·38 g) were separated from the phenols (0·22 g) and found to be only partly

[4] Kosak, *Experimentia* **10**, 69 (1954).

soluble in boiling light petroleum (A_2) (even C_{22} behenic acid is readily soluble in this solvent), and as shown below this fraction is a very complex mixture. Little information has so far been obtained on the acids insoluble in light petroleum but soluble in ether (A_3) and none on those insoluble in ether (A_1). From the acids soluble in light petroleum palmitic and one or two other acids have been separated in a pure form by conversion to methyl esters, followed by chromatography, distillation and hydrolysis. A vastly deeper insight into the composition of this fraction has been obtained, however, through the kindness of the Research Director of Unilever, Limited, Port Sunlight, where Mr. J. Clifford, by a combination of chemical methods followed by vapour-phase chromatographic analysis of the methyl esters, has obtained the results shown in Table 2.

Phenols

Dry tobacco leaves are said to contain on an average 2·7 per cent of their weight of phenols and tannins, including chlorogenic acid, and, although Commins and Lindsay[5] identified phenol, the three cersols and dihydroxybenzenes, and 1- and 2-naphthols in cigarette smoke by means of the ultra-violet peaks of their methyl esters, no one seems to have realised the extent or complexity of the phenolic mixture in the smoke.

Thus the 0·22 g of phenols (Example 1, Table 1, column 5, from 89 cigarettes) contains 0·21 g of ether-soluble material, of which 0·11 g is easily volatile in steam, leaving 0·1 g of *C* in the distilling flask. The 0·11 g on distillation gave 0·09 g, b.p. 50–55°/2 mm of *A* and the remainder up to 90°/2 mm of *B*.

The Research Dept. of I.C.I., Ltd., Dyestuffs Division, has very kindly examined these fractions by gas–liquid chromatography and the mass-spectrometer and they report that *A* consists of phenol (50–60 per cent), *o*-cresol (10 per cent), *m*- and *p*-cresols (20 per cent) and guaiacol (10 per cent) with small amounts of three other substituted phenols. In addition to small amounts of the above, *B* contains several more complex compounds, including three of the hydroaromatic type such as tetrahydro-2-naphthol. Fraction *C* consists of more complex phenols and neither gas–liquid chromatography or infra-red spectroscopy shed light on its composition. The mass-spectrometer examination of the fractions obtained at 250° and 350° (the materials are stable under these conditions) gave a large number of peaks. At the lower masses the groups of peaks are separated by mass 14 (i.e. CH_2), whilst in the 350° fraction the outstanding peak was at mass 272 with other prominent ones at 298 and 342. The 272 peak could be due to quite a number of polycyclic phenols, including a dihydroxybenzopyrene.

The benzene-soluble material not extracted by sodium hydroxide

This was extracted successively three times with 10% acetic acid and then three times with 10% hydrochloric acid to remove remaining basic substances. (Most of the nicotine is present in the aqueous acidic solution (column 4).) Then the esters present in the mixture were hydrolysed by being heated under reflux with methanolic potash and the neutral mixture M_N was obtained (see Table 1).

The alcohols liberated in the hydrolysis are also a considerable mixture, including

[5] B. T. Commins and A. J. Lindsay, *Brit. J. Cancer* **10**, 504 (1956).

crystalline ones, but only the simplest—b.p. 90°/2 mm—has been analysed so far (Found: C, 83·0, 83·07, 83·1; H, 10·5, 10·8, 10·8; mol. wt., 210, 230. $C_{16}H_{24}O$ requires: C, 82·8; H, 10·3 per cent; mol. wt., 232. $C_{18}H_{28}O$ requires: C, 83·1; H, 10·8 per cent; mol. wt., 260). Its reduction has not been examined and so no deduction can be made as to its ring nature.

In Example 9 (Table 1) the English cigarettes have been extracted with methanol before smoking, whereby 43·7 per cent of the weight of the tobacco is removed, of which 39 per cent is water soluble. The "tobacco" remaining on "smoking" gives practically no methanol-volatile materials and only little hentriacontane. The high proportion of the weight of a cigarette soluble in water will be due mainly to carbohydrate-type materials, and this 39 per cent when smoked will be responsible for many of the products found in *M*. It is stated that the higher the carbohydrate content the better the cigarette! Cigar tobacco contains very little carbohydrate materials. Unfortunately the literature contains little exact knowledge on the carbohydrates or terpenoids in tobacco and none, so far as I am aware, on their subjection to 770°, approximately the temperature in the glow of a cigarette.

CONCLUSIONS

It has been shown that the acidic and phenolic constituents of cigarette smoke (Example 1) form a very complex mixture (and M_N is no less complex) and, whilst the 3:4-benzopyrene content of smoke is much too little to account for its postulated action, insufficient attention has been given to other potentially harmful compounds present in considerable amounts.

Attention is now called briefly to the possibility that some of the acidic and phenolic constituents might account for many of the observed results. Broadly speaking, heavy cigarette smokers in cities show, after some years, a greater incidence of lung cancer than similar smokers in rural areas and a very much greater incidence than non-smokers. That some of the latter fall victims is to be expected when fully one-third of the smoke of a cigarette drifts from its burning end and affects those within reach, particularly on public transport.

Other variations such as shown by the United States–United Kingdom statistics on lung cancer and the Russian claim to immunity will probably only be explained when the nature of the constituents of the various smokes is fully known and their actions on living cells understood.

It is known that some aromatic hydrocarbons are soluble in acids and it has now been found that formic acid exerts a selective solvent action on some hydrocarbons in mixtures. The lungs of city dwellers particularly are soot covered and we showed[6] that city smoke contained at least one potent carcinogen that is not benzopyrene. It has been claimed that carcinogens absorbed on soot are inactive, but since 50% acetic acid and cold propionic and butyric acids will dissolve appreciable amounts of benzopyrene and acetic acid will also extract the above-mentioned carcinogenic agent from soot, it could, therefore, elute such a carcinogen from lung soot and thus render it active.

As for the phenol present (at least 1 mg per cigarette with the cresols and possibly considerably more, since these compounds being appreciably soluble in water would

[6] G. R. Clemo, E. J. Miller and F. C. Pybus, *Brit. J. Cancer* **9**, 137 (1955).

probably be partly removed in the water extraction under Column 4), its irritant and corrosive action is universally recognised. It could largely explain the bronchitic action of cigarette smoke and also render lung sites susceptible to attack by other smoke constituents even if its prolonged irritant action did not itself produce cancer.

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PARTIAL HYDROLYSIS OF DIETHYL γγ-DIETHOXYCARBONYLPIMELATE: A METHOD OF PREPARING γγ-DIETHOXYCARBONYLPIMELIC ACID

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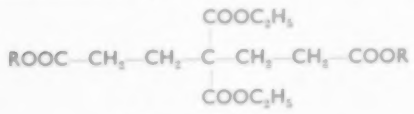
Abstract—When one mole of diethyl γγ-diethoxycarbonylpimelate was hydrolysed with exactly two moles of sodium hydroxide in absolute ethanolic solution at room temperature, γγ-diethoxycarbonylpimelic acid was produced in excellent yield. Its structure was proved beyond doubt by two independent methods.

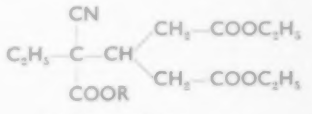
γγ-DIETHOXYCARBONYLPIMELIC ACID (II), which was required for future synthetic work, can be prepared by partial hydrolysis of diethyl γγ-diethoxycarbonylpimelate (I). It has been shown to be a dibasic acid and its structure was proved by synthesis of dibenzyl γγ-diethoxycarbonylpimelate (III) by condensing diethyl malonate with benzyl β-bromopropionate, which was reduced catalytically with hydrogen to yield (II). The partial hydrolysis of (I) was shown to have occurred selectively, if not solely, on both unhindered ester groups at the end of the molecule, so leaving two malonic ester groups intact.*[1]

In the mean time Evstigneeva *et al.*,[2] in their brilliant synthesis of emetine, showed that when hydrolysed by one molecular equivalent of sodium hydroxide in absolute ethanol, triethyl α-cyano-α-ethyl-β-(carboxymethyl)glutarate (IV) gave preferentially he acid (V). In this case, therefore, the ester group that was hydrolysed was the hindered one and this seemed to contradict the result obtained by Sugasawa and Sakurai.[1] Thus it appeared desirable to provide additional evidence for the structure of the acid (II).

Blanc[3] cyclised 3:3-dimethylpimelic acid with loss of carbon dioxide to 4:4-dimethyl*cyclo*hexanone by treatment with acetic anhydride, and (II) on similar treatment was cyclised to 4:4-diethoxycarbonyl*cyclo*hexanone (VI), which was characterised by its semicarbazone and 2:4-dinitrophenylhydrazone. To prove the



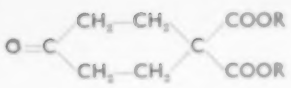
I: R = $-C_2H_5$
II: R = $-H$
III: R = $-CH_2-C_6H_5$



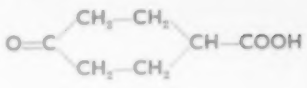
IV: R = $-C_2H_5$
V: R = $-H$

* Previously published by Sugasawa and Sakurai[1] in Japanese. The preparation of (II) is now described in English.

[1] S. Sugasawa and K. Sakurai, *J. Pharm. Soc. Japan*, **62**, 82 (1942).
[2] R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. I. Zakharkin, and N. A. Preobrazhenskii, *Chem. Abst.* **42**, 5949 (1948).
[3] G. Blanc, *C. R. Acad. Sci., Paris* **144**, 143 (1906).



VI: R = $-C_2H_5$
VII: R = —H



VIII

structure of (VI) beyond doubt, it was hydrolysed with alkali to give 4-oxo*cyclo*hexanedicarboxylic acid (VII), which has previously been described.[4] (VII) on being heated at 160° gave 4-oxo*cyclo*hexanecarboxylic acid (VIII), previously prepared by Martin and Robinson.[5]

EXPERIMENTAL

γγ-Diethoxycarbonylpimelic acid (II). An absolute ethanolic sodium hydroxide solution containing 0·2 g (0·05 mole) of sodium hydroxide was prepared by dissolving 1·15 g (0·05 mole) of metallic sodium in 50 ml of absolute ethanol to which 0·9 ml of water had been added. Diethyl γγ-diethoxycarbonylpimelate (I) (8·7 g, 0·024 mole) was then added to this solution with shaking to give a clear solution, which was set aside at room temperature (ca. 18°) for 20 hr, when a white solid separated. Sufficient water to dissolve this solid was now added to give a clear solution, from which the ethanol was removed *in vacuo* at room temperature. The residual solution was filtered and the filtrate was acidified carefully with dilute hydrochloric acid with cooling. The whole was kept in an ice-chest, when a white crystalline substance separated, which was filtered off and washed with a little cold water. This compound, m.p. 118–121°, was purified by recrystallisation from benzene to give colourless plates (6·5–6·7 g, 90–92 per cent), m.p. 123-123·5°. (Found: C, 51·2; H, 6·6; COOH, 29·8. $C_{11}H_{18}O_4(COOH)_2$ requires C, 51·3; H, 6·6; COOH, 29·6 per cent).

The acid is stable on being heated to 180° without decomposition and colour change, and this stability toward heat suggests that both malonic ester groups remain intact.

Dibenzyl γγ-diethoxycarbonylpimelate (III). Metallic sodium (1 g, 0·043 mole) was finely powdered in dry xylene and to this suspension was now added diethyl malonate (3·52 g, 0·022 mole). The mixture was vigorously shaken to form a white pasty mass. Benzyl β-bromopropionate (9·5 g, 0·043 mole), a colourless oil of $b.p._{\cdot 6}$ 133–135°, was added with shaking and the mixture was heated on a steam-bath for 6–7 hr with stirring, when a neutral solution resulted. Xylene was removed by steam-distillation and the oily residue was taken up in ether, washed, dried and evaporated. The remaining oil distilled at 155–158°/0·05–0·06 mm, as a pale-yellow viscous syrup (5·1 g, 48·1 per cent) (Found: C, 66·7; H, 6·4. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·7 per cent).

γγ-Diethoxycarbonylpimelic acid (II). The dibenzyl ester (III) (1 g) in ethanol was reduced with hydrogen activated over Adams's platinum catalyst, when about 90 ml of hydrogen, corresponding roughly to two moles, was smoothly absorbed. After being worked up as usual, a crystalline solid was obtained, which formed colourless plates, m.p. 123°, from benzene and was proved to be identical by mixed melting point with the specimen prepared by partial alkaline hydrolysis.

Diethyl 4-*oxo*cyclo*hexanedicarboxylate* (VI). γγ-Diethoxycarbonylpimelic acid

[4] E. Hardeggar, Pl. A. Plattner and F. Blanc, *Helv. Chim. Acta* **24**, 796 (1944). M.p. 147·5–149·5° according to these authors.
[5] R. H. Martin and R. Robinson, *J. Chem. Soc.* 496 (1943).

(II) (3·5 g) was dissolved in 10 ml of acetic anhydride containing 1 ml of pyridine. The mixture was gently heated under reflux in an oil-bath for 2 hr, during which time the evolution of carbon dioxide had occurred and ceased. After removal of acetic acid and excess of actic anhydride *in vacuo*, the residue was subjected to vacuum distillation, to give a colourless oil of camphor-like fragrance (2·6 g, 93 per cent), b.p.$_{6}$ 141°.

The semicarbazone was obtained as colourless spheroidal crystals from ethanol, m.p. 185–186° (Found: C, 52·5; H, 7·0; N, 13·6. $C_{13}H_{21}O_5N_3$ requires C, 52·2; H, 7·1; N, 14·0 per cent).

The 2:4-dinitrophenylhydrazone was obtained as yellow needles from ethanol, m.p. 119° (Found: C, 50·9; H, 5·0; N, 13·6. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·25; N, 13·3 per cent).

4-*Oxo*cyclo*hexanedicarboxylic acid* (VII). (VI) (1·5 g) was hydrolysed by being heated on a steam-bath with sodium hydroxide in aqueous ethanol. Ethanol was then removed by distillation, the residue was dissolved in water, and the solution was filtered through a wet filter-paper. The filtrate was acidified with dilute hydrochloric acid and thoroughly extracted with ether, dried and evaporated. The solid obtained was purified from acetone–benzene, to give colourless needles (1 g), m.p. 149–150° (dec.).

4-*Oxo*cyclo*hexanecarboxylic acid* (VIII). (VII) (1 g) was heated at 160° for 10 min and was then distilled. The distillate (0·65 g), b.p. 129°/2 mm, solidified on standing. This forms colourless needles, m.p. 67°, after recrystallisation from ether–light petroleum (Found: C, 59·5; H, 7·0. $C_7H_{10}O_3$ requires C, 59·1; H, 7·1 per cent).

The 2:4-dinitrophenylhydrazone was obtained as golden yellow needles from ethanol, m.p. 191–192° (dec.).

An authentic sample of 4-oxo*cyclo*hexanecarboxylic acid was prepared from ethyl *p*-hydroxybenzoate by the method of Martin and Robinson.[5] This acid melted at 67° alone or admixed with the one obtained above, and formed a yellow 2:4-dinitrophenylhydrazone having the same melting point.

Tetrahedron, 1958, Vol. 3, p. 178. Pergamon Press Ltd., London

BOOK REVIEW

VATRKES MIGRDICHIAN: **Organic Synthesis,** Vols. I and II. Reinhold, New York, 1957. 1500 pp., 280s.

ORGANIC synthesis is such a vast subject that to attempt to compress it, as does Dr. MIGRDICHIAN, into about 1,000 pp. of text is manifestly impossible. Indeed, the magnitude of the task is so great that it is doubtful if any one man—however dedicated he might be—could hope to succeed. The two volumes under review represent a compromise between a detailed text of synthetic methods, which would run to many volumes, and a series of general, but critical, essays. It cannot be claimed that the end product is a resonance hybrid of the two ideal states. Whilst many factual statements are strung together, the coverage does not appear to be complete in any section and the treatment appears to be quite uncritical. The literature is covered, one would judge from the lists of references, up to the end of 1952, although the author does not state this in the preface.

In the light of these facts, the claim on the dust jacket that these volumes constitute "the most systematic, fully integrated and up-to-date presentation of organic synthesis in all its aspects ever published. This truly monumental work is so complete and so precise in its coverage of the subject that it surpasses even specialized texts in each and every phase of this vast field" can scarcely be maintained. If the author had been more modest in his objective and, in particular, more critical in his survey of the literature, the work would have been more worthwhile.

The arrangement of the subject matter is logical. Vol. I deals with open-chain saturated compounds, Vol. II with open-chain unsaturated, with alicyclic and with aromatic compounds. Vol. I includes useful sections on organo-metallic compounds. Each chapter is documented with references which should be valuable as starting points for further literature searches. The research worker may well find it useful to secure a general background from these two volumes before consulting more specialized texts or the literature. The volumes are well printed and free from trivial errors.

Whilst these volumes may not be as significant as the claims made for them would suggest, nevertheless they will find a place in many libraries. The reader cannot but respect the industry and effort of the author. If the author has failed in his objective, it is not through his own faults, but simply because the task chosen was so great as to defeat even a Hercules.

D. H. R. BARTON

Publisher's Notice to Contributors

It is regretted that due to a rather unexpectedly large increase in the number of manuscripts submitted for publication in *Tetrahedron* towards the end of last year, the time taken to publish a manuscript increased to approximately 7 months. Steps have now been taken to ensure that the delay in publication shall not exceed 5 months and will be considerably less for short papers or Letters to the Editor, which normally will be published within 30–60 days.

Papers to be published in future issues

D. H. Whiffen and D. Steele: Carbon–hydrogen stretching vibrations in fluoro*cyclo*hexanes.

W. Langenbeck: Über organische Katalysatoren—L. Entwicklungslinien der organischen Katalysatoren.

F. Scardiglia and J. D. Roberts: Reactions of non-activated amyl halides with nucleophilic agents induced by alkali amides in liquid ammonia.

R. D. Wilson: Naphthaquinones—I. The molecular structures of some halogeno-2:7-dihydroxynaphthalenes.

A. K. Ganguly, T. R. Seshadri, and P. Subramanian: A study of leucoanthocyanidins of plants—I. Isomers of leucodelphinidin from Karada bark and eucalyptus gum.

R. Aneja, S. K. Mukerjee and T. R. Seshadri: Synthesis of benzo-furan derivatives—II. A new synthesis of visnagin.

A. Seigel, F. Wessely, P. Stockhammer, F. Antony und P. Klezl: Über die Einwirkung von Alkalihydroxydlösungen auf *o*-Chinolacetate.

R. Fusco and S. Rossi: Asymmetric triazines—XIII. Reaction of phosphorus pentachloride with 4-nitrosopyrazoles.

L. H. Briggs and R. C. Cambie: The extractives of *Vitex lucens*.

C. Djerassi and O. Halpern: Macrolide antibiotics—VII. The structure of neomethymycin.

K. Weisner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis: Annotinine—II. The complete structure.

H. Hirschmann and F. B. Hirschmann: C-22 ketals related to the sapogenins.

T. Kubota: Volatile constituents of black rotted sweet potatoes.

V. M. Micović and A. Stojiljković: The condensations of polyhydric alcohols and monosaccharides with *cyclo*pentanone and *cyclo*hexanone.

B. Helferich und M. Burgdorf: Über Derivate der *D*-Xylose.

E. Leete: The biogenesis of annotinine.

D. Lloyd and J. S. Sneezum: The preparation of some pyridinium *cyclo*pentadienylides.

D. H. Reid: Stable π-electron systems and new aromatic structures.

C. R. Patrick: Some aspects of the thermochemistry and thermodynamics of fluorocarbons.

C. Chiurdoglu et J. Decot: Contribution à l'étude des composés sesquiterpeniques—II. Étude de la structure du bi*cyclo*vétivénol et du tri*cyclo*vétivénol, alcools primaires de l'essence de vetiver.

H. M. Smith, J. M. Smith and F. S. Spring: The triterpenoids—LVI. The chemistry of the soyasapogenols A, B and C.

I. Chmielewska, J. Cieślak, K. Gorczyńska, B. Kontnik et K. Piakowska: Structure de la yangonine. Étude spectrographique dans l'ultraviolet et l'infrarouge.

P. Crabbe, G. Ourisson et T. Takahashi: Le Diptérocarpol—I. Preparation de la 8:14-dimethyl 18-nortesterone.

J. F. Biellmann, P. Crabbe et G. Ourisson: Le Diptérocarpol—II. Stéréochimie en C-13 et en C-17.

P. K. Grover and T. R. Seshadri: Preparation and constitution of *iso*pinastric acid.

E. Clar, W. Kemp and D. G. Stewart: The significance of Kekulé structures for the stability of aromatic systems.

M. L. Scarpati and G. Oriente: Chicoric acid (dicaffeyltartaric acid) its isolation from chicory (*Chicorium intybus*) and synthesis.

J. C. EARL: Bond character, bond order and the quadrivalency of carbon.

S. G. SMITH and S. WINSTEIN: Sulfoxides as nucleophiles.

C. A. BARSON and J. C. BEVINGTON: A tracer study of the benzoyloxy radical.

B. C. SAUNDERS and B. P. STARK: Studies in peroxidase action. Transiodination reactions and related processes.

M. LORA TAMAYO: Some results obtained in the utilisation of quinones as philodiene.

I. CHMIELEWSKA and V. CIEŚLAK: Vitamins and antivitamins *K* tautomerism of dicoumarol.

F. SPARATORE, R. GREENHALGH and L. MARION: A suggested structure for delsoline.

W. VON E. DOERING, H. G. BOYNTON, H. W. EARHART, G. LABER, M. SAUNDERS and E. F. WADLEY: The 1,1,2,3,4,5,6-heptamethylbenzenonium ion.

S. E. FLORES, J.HERRÁN and H. MENCHACA: The synthesis of penduletin.

L. VELLUZ, B. GOFFINET et G. AMIARD: Sur le comportement photochimique des 19-nor $\Delta^{3,5}$steroides.

SHIGEHIKO SUGASAWA and RYUJI TACHIKAWA: Extension of Bischler–Napieralski reaction—I. Synthesis of *iso*quinoline derivatives. A synthesis of rac-apomorphine dimethyl ether.

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Tetrahedron, 1958, Vol. 3, pp. 181–184. Pergamon Press Ltd., London

CARBON–HYDROGEN STRETCHING VIBRATIONS IN FLUORO*CYCLO*HEXANES

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(*Received* 11 *October* 1957)

Abstract—For perfluoro*cyclo*hexane derivatives in which not more than one fluorine at each carbon atom is replaced by a hydrogen atom, it is established that C–H groups with an axial hydrogen show infra-red absorption at 2980 cm^{-1} and with equatorial hydrogen at 2974 cm^{-1}. With 1H/2H-, 1H:2H/- and 1H:3H/-decafluoro*cyclo*hexane the frequencies are reduced somewhat. When the C–H groups are adjacent to a double bond the absorption is at 2961 cm^{-1}, while olefinic C–H groups absorb near 3095 cm^{-1} in the fluorocarbon series. The C–H absorption is at 3102 cm^{-1} in pentafluorobenzene.

MANY perfluoro*cyclo*hexane derivatives have recently become available[1–5] for infra-red spectral investigation* and when provided several of their structures were uncertain. In order to establish spectral correlations which might be useful in structure determination, it was decided to measure the carbon–hydrogen stretching frequencies near 3000 cm^{-1} under high resolution to see if hydrogen atoms in the axial and equatorial positions could be differentiated.

RESULTS

Table 1 shows the frequencies and approximate extinction coefficients in the gas phase. The boiling points are given to aid identification with the literature[1–5] where the preparation and the structure determinations are discussed. The second column of the table indicates the axial, *a*, equatorial, *e*, or olefinic, *o*, nature of the hydrogen atoms in the order quoted in the name. For the polyhydro compounds the numbering of the hydrogen atoms on one side of the *cyclo*hexane ring are given in front of the solidus and the substituents *trans* to these, thereafter.

DISCUSSION

For the saturated compounds at the head of Table 1 the carbon–hydrogen stretching frequency lies in the narrow range 2968 to 2984 cm^{-1}, and it would seem that the variation between axial and equatorial substituents is much less than in the deuterated steroids[7] where the axial C–D links are found to absorb about 40 cm^{-1} below the equatorial. Nevertheless a closer inspection shows that an isolated axial hydrogen,

* The full spectra will be submitted to the Documentation of Molecular Spectroscopy punched card collection. Comparison of the spectra of dodecafluoro*cyclo*hexane and undecafluoro*cyclo*hexane confirm that the sample of the former used by Rowlinson and Thacker[6] contained some of the undecafluoro-body indicated by absorption at 730, 830 and 943 cm^{-1} as these authors themselves suggest.

[1] R. P. Smith and J. C. Tatlow, *J. Chem. Soc.* 2505 (1957)
[2] D. E. M. Evans, J. A. Godsell, R. Stephens, J. C. Tatlow and E. H. Wiseman, *Tetrahedron* **2**, 183 (1958).
[3] J. A. Godsell, M. Stacey and J. C. Tatlow, *Tetrahedron* **2**, 193 (1958).
[4] G. B. Barlow, M. Stacey and J. C. Tatlow, *J. Chem. Soc.* 6090 (1955).
[5] R. Stephens and J. C. Tatlow, *Chem. & Ind.* 821 (1957).
[6] J. S. Rowlinson and R. Thacker, *Trans. Faraday Soc.* **53**, 1, (1957).
[7] E. J. Corey, R. A. Sneen, M. G. Danaher, R. L. Young and R. L. Rutledge, *Chem. & Ind.* 1294 (1954).

TABLE 1

Name		cm^{-1}	ε	Boiling point
Saturated				
Undecafluoro*cyclo*hexane	*a*	2979	8	63°C
1H/2H-decafluoro*cyclo*hexane	*a*/*a*	2977	12	70
1H:2H/- „ „ „	*a*:*e*/	2974, 2969	10, 6	91
1H/3H- „ „ „	*a*/*e*	2979, 2973	15, 3	78
1H:3H/- „ „ „	*a*:*a*/	2974	20	89
1H/4H- „ „ „	*a*/*a*	2980	15	78
1H:4H/- „ „ „	*a*:*e*/	2979, 2973	11, 11	86
1H/2H:4H-nonafluoro*cyclo*hexane	*a*/*a*:*a*	2983, 2974	5, 20	101
1H:4H/2H- „ „	*a*:*e*/*a*	2984, 2979, 2973	9, 10, 9	93
1H:2H/4H- „ „	*a*:*e*/*a*	2979, 2974	12, 10	107
1H:2H:4H/- „ „	*e*:*a*:*a*/	2973, 2968	10, 8	136
1H:4H/2H:5H-octafluoro*cyclo*hexane	*a*:*e*/*a*:*e*	2979, 2974, 2970	10, 15, 8	118
*1CF_3/4H-tridecafluoromethyl-*cyclo*hexane	/*e*	2974	9	88 II[a]
*1CF_3:4H/- „ „ „	*e*/	2981	11	88 I[a]
Mono-olefines				
1H-nonafluoro*cyclo*hexene	*o*	3104, 3073	7, 4	63
3H- „ „	*x*	2961	8	69
4H- „ „	(*a*)	2983	8	71
1H:2H-octafluoro*cyclo*hexene	*o*:*o*	3085	liq.	87
3H/4H- „ „	*x*/(*a*)	2980, 2962	9, 7	86
3H:4H/- „ „	*x*:(*a*)/	2979, 2960	7, 7	116
4H/5H- „ „	(*a*)/(*a*)	2977, 2970	10, 8	90
4H:5H/- „ „	(*a*):(*e*)/	2979, 2975	8, 8	99
1H:5H- „ „	*o*:(*a*)	3102, 3067, 2980	3, 6, 8	85
Polyenes				
1H-heptafluoro*cyclo*hexa-1:3-diene	*o*	3113, 3084	15, 4	72
2H- „ „	*o*	3098	6	76
1H-heptafluoro*cyclo*hexa-1:4-diene	*o*	3097	8	67
*1H:4H-hexafluoro*cyclo*hexa-1:4-diene	*o*:*o*	3087	19	—
*1H:5H- „ „ „	*o*:*o*	3082	19	71
Pentafluorobenzene	*ar*	3102	4	89

a = axial, (*a*) = pseudoaxial, *e* = equatorial, (*e*) = pseudoequatorial, *o* = olefinic, *x* = adjacent to double bond, *ar* = aromatic.
* These structures are not yet proved by chemical means, but are based on the methods of preparation and the infra-red spectra.

as in undecafluoro-, 1H/3H-, 1H:4H/- or 1H/4H-decafluoro*cyclo*hexane, absorbs at 2980 ± 2 cm^{-1} and that an isolated equatorial hydrogen absorbs at 2974 ± 2 cm^{-1}, as in the 1H/3H- and 1H:4H/-decafluoro*cyclo*hexanes. Indeed the identification between the *cis*/*trans* 1H:4H-isomers was originally made on the grounds that the first isomer obtained showed two overlapping bands and was therefore unlikely to be the *trans*-isomer which would be centrosymmetric and have only one infra-red active C–H stretch. This expectation was confirmed when the *trans*-isomer became available

and shown to have only one band: the identification has subsequently[3] been confirmed by dipole moment measurements. Based on the infra-red differentiation between axial and equatorial hydrogen atoms, it is possible to identify the isomers of 4H-tridecafluoromethyl*cyclo*hexane.[4,5] The bulky trifluoromethyl group in these compounds will ensure that the molecules adopt that conformation of the *cyclo*hexane ring in which the $—CF_3$ group is lying equatorially. A *trans*-hydrogen atom at position 4 must also be equatorial and would absorb at 2974 cm^{-1} as observed for the isomer designated[5] II, whereas a *cis*-hydrogen at position 4 would be axial and the observed absorption at 2981 cm^{-1} for isomer I is in accord with the predicted 2980 cm^{-1} for this arrangement.

The frequencies given above for axial and equatorial hydrogens are shifted slightly when two hydrogens are on adjacent atoms in the ring or are both in axial positions on the same side of the plane of the ring. In the 1H/2H-compound one band is observed at 2977 cm^{-1} which is only 3 cm^{-1} from the expected position since both hydrogens are axial. This will be the out-of-phase C–H stretch, as the in-phase vibration will be almost inactive in the infra-red since the dipole moment change would, from symmetry considerations, be parallel to the twofold symmetry axis and consequently approximately perpendicular to the C–H bonds which are stretching. With 1H:2H/-decafluoro*cyclo*hexane the decrease in frequency is slightly greater and the bands are at 2974 and 2969 cm^{-1}; in this compound the hydrogens are closer together in space and it is perhaps a consequence of this that the frequencies move towards the hydrocarbon values. The hydrogens are also close in space in the 1H:3H/-compound in which they occupy axial positions on the same side of the ring plane and the frequency is again reduced about 6 cm^{-1} to 2974 cm^{-1}. In this case the single band observed will be the in-phase motion, since the out-of-phase motion must produce a dipole moment change perpendicular to the plane of symmetry and approximately perpendicular to the C–H bonds and so be very weak.

Experience with the 1H:2H:4H-nonafluoro*cyclo*hexanes suggests that their C–H stretching frequencies are governed by similar rules. Except when involved in 1H:2H/- or 1H:3H/-structures the C–H absorptions remain near 2980 cm^{-1} when axial, and 2974 cm^{-1} when equatorial, with a slight lowering for the 1H/2H-system. Again the characteristic frequency for the 1H:3H/-structures is 2974 cm^{-1} when diaxial and the 1H:2H/-arrangement again gives a pair of bands near 2974 and 2969 cm^{-1}. For example 1H/2H:4H-nonafluoro*cyclo*hexane (*a*/*a*,*a*) has absorption at 2974 cm^{-1} attributable to the 1 : 3 diaxial structure of hydrogens on $C_{(2)}$ and $C_{(4)}$; this band is about double the intensity of that at 2983 cm^{-1} which must be attributed to the isolated axial hydrogen on $C_{(1)}$.

In the fluoro*cyclo*hexene series there is seen from Table 1 to be a possibility of distinguishing hydrogen substitution at positions 4 and 5 from that at 3 and 6. The conformation will be the usual half chair form and the local arrangement at positions 4 and 5 is hardly to be distinguished from that in the *cyclo*hexane series; the substituents are normally designated pseudo-axial and pseudo-equatorial. It is to be expected that the hydrogen atoms will prefer the pseudo-axial position and this is consistent with the frequency of 2983 cm^{-1} in 4H-nonafluoro*cyclo*hexene. The three *cyclo*hexene derivatives with the hydrogen at position 3 absorb at 2960, 2961 and 2962 cm^{-1} respectively, and absorption at 2961 cm^{-1} must be considered characteristic

[5] R. P. Smith, Ph.D. Thesis, University of Birmingham.

for substitution at this position. Indeed when first available the 3H:4H/- and 4H:5H/-octafluoro*cyclo*hexenes were merely known to be products of dehydrofluorination of 1H:2H/4H-nonafluoro*cyclo*hexane and these structures were suggested from the infrared spectra and their confirmation by chemical methods consequently accelerated. In assigning structures the 3H-absorption in the *cyclo*hexenes at 2961 cm^{-1} was especially valuable.

Olefinic hydrogens appear to absorb in the range 3070 to 3120 cm^{-1} according to the type of unsaturated system and the point of attachment thereto. There are insufficient examples to indicate the exact pattern to be expected except to comment that hydrogen attached to a 1:3-diene system absorbs at the upper end of this range and that in some cases the band was unexpectedly split, possibly by Fermi resonance. In the one case examined with hydrogens attached at both ends of a double bond, 1H:2H-octafluoro*cyclo*hexene, the absorption was too weak to measure accurately in the vapour.

In pentafluorobenzene the C–H stretching frequency at 3102 cm^{-1} is slightly higher than the fundamental frequencies of 1:2:4:5-tetrafluorobenzene[8,9] at 3097 cm^{-1} (A_g) and 3088 cm^{-1} (B_{1u}).

It is clear that in all these compounds the presence of the fluorine raises the C–H stretching frequency by about 70 cm^{-1} compared with the hydrocarbons. Taking average hydrocarbon frequencies[10,11] the comparison shown in Table 2 is obtained. The frequency shifts are probably electronic in origin.

TABLE 2

	Hydrocarbon	Fluorocarbon	Difference
Naphthenic C–H	2890 cm^{-1}	2980 cm^{-1}	+90 cm^{-1}
Olefinic C–H	3020 cm^{-1}	3080 cm^{-1}	+60 cm^{-1}
Aromatic C–H	3040 cm^{-1}	3100 cm^{-1}	+60 cm^{-1}

EXPERIMENTAL

The compounds were measured in the gas phase in a 10 cm absorption cell using a 2500 l.p.i. N.P.L. replica grating of size 6 in. × 6 in. in the third order on the spectrometer previously described.[12] The frequencies are thought to be correct to ±2 cm^{-1} the chief error being that of locating the centre of the wide bands, especially when they overlap. The extinction coefficients[11], ε, are maximum values for non-overlapping bands and are approximate estimates of the separate intensities for overlapping bands; they are quoted to indicate relative intensities in each compound.

Acknowledgements—We wish to thank Dr. J. C. Tatlow and his co-workers Drs. D. E. M. Evans, J. A. Godsell, R. P. Smith, R. Stephens and Messrs. E. Nield and E. H. Wiseman for providing the compounds and for many discussions. We also wish to thank Professor M. Stacey for his interest in the work and Dr. L. A. Sayce for making the grating available. D. S. wishes to acknowledge the receipt of a University Appeal Scholarship.

[9] E. E. Ferguson, R. L. Hudson, J. R. Nielsen and D. C. Smith, *J. Chem. Phys.* **21**, 1464 (1953).
[10] L. J. Bellamy, *Infra-red Spectra of Complex Molecules*. Methuen, London (1954).
[11] R. N. Jones and C. Sandorfy, *Techniques of Organic Chemistry* p. 247, Vol. 9. Interscience, New York (1956).
[12] H. Spedding and D. H. Whiffen, *Proc. Roy. Soc.* A **238**, 245 (1956).

Tetrahedron, 1958, Vol. 3, pp. 185–196. Pergamon Press Ltd., London

ÜBER ORGANISCHE KATALYSATOREN—L

ENTWICKLUNGSLINIEN DER ORGANISCHEN KATALYSATOREN

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IM Frühjahr 1927 erschien meine erste Arbeit über organische Katalysatoren,[1] und seitdem haben meine Mitarbeiter und ich etwa 50 Abhandlungen auf diesem Gebiete veröffentlicht. Es ist deshalb an der Zeit, einmal Rückschau zu halten und festzustellen, was in diesen 30 Jahren erreicht worden ist, und welche Ausblicke sich für die Zukunft ergeben. 50 Veröffentlichungen sind bei dem heutigen Umfang der chemischen Publizistik nicht viel. Man muss dabei aber berücksichtigen, dass es sich seinerzeit um ein fast ganz neues Arbeitsgebiet handelte, und dass wir anfangs über den einzuschlagenden Weg völlig im Unklaren waren. Heute zeichnen sich gewisse systematische Linien ab, die als Wegweiser dienen können, aber es gibt noch keineswegs gebahnte Landstrassen, die zu einer Massenproduktion von Veröffentlichungen führen. Das ist aber andererseits gerade der Reiz unseres Arbeitsgebietes. Deshalb wird heute in zunehmendem Masse auch in anderen Laboratorien über organische Katalysatoren gearbeitet.

Unter organischen Katalysatoren haben wir von Anfang an organische Stoffe mit katalytischer Wirkung verstanden, die nicht Enzyme sind. Meist handelte es sich um verhältnismässig einfache synthetische Verbindungen, gelegentlich aber auch um kompliziertere nichtenzymatische Naturstoffe, wie etwa die Blutfarbstoffe. Wir kennen heute mehrere Gruppen von organischen Katalysatoren, die sich hauptsächlich durch die Art der Zwischenstoffe voneinander unterscheiden, die sie mit ihren Substraten bilden. Bisher gibt es folgende:

(1) Hauptvalenzkatalysatoren enthalten aktive Gruppen,[2] die sich mit den Substraten durch feste aber sehr reaktionsfähige Atombindungen verknüpfen.

(2) Chelatkatalysatoren sind Chelate von Metallionen mit mehrzähnigen Komplexliganden. Anscheinend tritt das Substrat immer in diese Chelate ein, sodass auch die Zeischenstoffe Komplexverbindungen sind.

(3) Einschlusskatalysatoren haben in ihrem Molekül einen Hohlraum, in den sich das Substrat zu einer Einschlussverbindung einlagert und dabei aktiviert wird.

(4) Basische Katalysatoren sind organische Basen und lagern Protonen aus dem Substrat an.

Zu diesen vier Typen kommen noch eine Reihe von Kombinationen, z.B. gibt es Hauptvalenzkatalysen, die zugleich Basenkatalysen oder Chelatkatalysen sind.

Das ist gewissermassen ein Längsschnitt durch das Lehrgebäude der organischen Katalyse. Es gibt aber auch eine Art Querschnitt, aus dem man ersicht, mit welcher Zielsetzung organisch-katalytische Arbeiten ausgeführt werden können. Von solchen Zielen gibt es, wie bei allen organisch-chemischen Arbeiten, zur Hauptsache drei:

[1] W. Langenbeck, *Ber. Dtsch. Chem. Ges.* **60**, 930 (1927).
[2] W. Langenbeck, *Z. Elektrochem.* **54**, 193 (1950).

(1) Theoretische Arbeiten auf experimenteller Grundlage. Man versucht allgemeine Gesetzmässigkeiten zu finden z.B. über die Beziehungen zwischen Konstitution und Aktivität. Die Natur der Zwischenstoffe aufzuklären ist dabei von besonderer Bedeutung. Diese Zielsetzung bildet die notwendige Grundlage für die beiden folgenden.

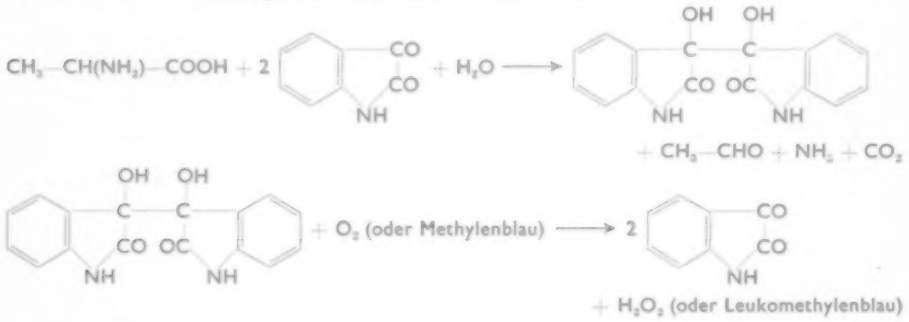
(2) Technische Arbeiten beschäftigen sich mit der Anwendung organischer Katalysatoren auf industrielle Probleme.

(3) Biochemische Arbeiten. Die organischen Katalysatoren werden als Fermentmodelle betrachtet und sollen dazu beitragen, den Chemismus der Fermentwirkung aufzuklären.

Wir wollen nun zunächst den Längsschnitt und dann den Querschnitt näher betrachten. Wegen der Knappheit des Raumes werden dabei hauptsächlich die Untersuchungen meiner Schüler berücksichtigt werden.

Hauptvalenzkatalysatoren

Der erste organische Katalysator in unserer Arbeitsreihe, das Isatin,[1] war ein Hauptvalenzkatalysator. Am Isatin wurde der Begriff neu entwickelt. Es dehydriert α-Aminosäuren nach folgendem vereinfachten Schema:

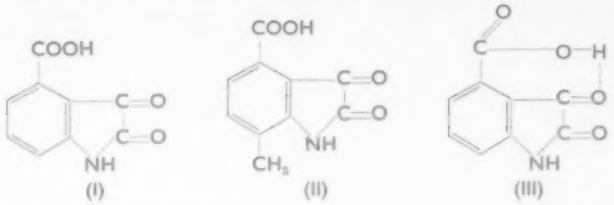


Nur ein ganz kleiner Teil der Aminosäuren, nämlich zwei Atome Wasserstoff werden vom Katalysator fest gebunden, aber trotzdem in einer Form, in der er gegen Sauerstoff oder Methylenblau sehr reaktionsfähig ist. Die beiden Substrate lösen ihn leicht wieder vom Katalysator ab. Dieser Mechanismus wurde mehrere Jahre vor der Entdeckung der Flavin- und Pyridinfermente gefunden. Die Modellversuche haben zweifellos dazu angeregt, in der lebenden Zelle nach ähnlichen Vorgängen zu suchen.

Bald zeigte es sich, dass die Aktivität stark von der Konstitution des Katalysators abhängt.[3-10] Führt man gewisse Substituenten an geeigneten Stellen des Isatinmoleküls ein (aktivierende gruppen), so steigt sie mehr oder weniger an. Solche Versuche wurden im Laufe der Jahre stetig fortgesetzt. Sie führten schliesslich zu den bisher aktivsten Isatinderivaten, der Isatin-4-carbonsäure (I) und der leichter

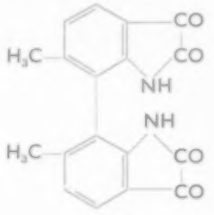
[3] W. Langenbeck, *Ber. Dtsch. Chem. Ges.* **61**, 942 (1928).
[4] W. Langenbeck, L. Weschky und O. Gödde, *Ber. Dtsch. Chem. Ges.* **70**, 672, 1039 (1937).
[5] W. Langenbeck, *Z. Elektrochem.* **46**, 106 (1940).
[6] W. Dethloff und H. Mix, *Chem. Ber.* **82**, 534 (1949).
[7] W. Dethloff und K. Schreiber, *Chem. Ber.* **83**, 157 (1950).
[8] H. Mix, *Liebigs Ann.* **592**, 146 (1955).
[9] W. Langenbeck, K. Rühlmann, H. H. Reif und F. Stolze, *J. Prakt. Chem.* **4**, 136 (1956).
[10] H. Mix und H. W. Krause, *Chem. Ber.* **89**, 2630 (1956).

zugänglichen 7-Methyl-isatin-4-carbonsäure (II). Diese Stoffe wirken am besten in einem basischen Lösungsmittel, z.B. in wässrigem Pyridin. Wir haben hier den ersten Fall einer kombinierten Hauptvalenz-Basenkatalyse. Die freie Carboxylgruppe ist für die maximale Wirkung erforderlich. Die Ester, Amide usw. sind weniger aktiv. Vielleicht wirkt die Ausbildung einer Wasserstoffbrücke so besonders günstig (III).



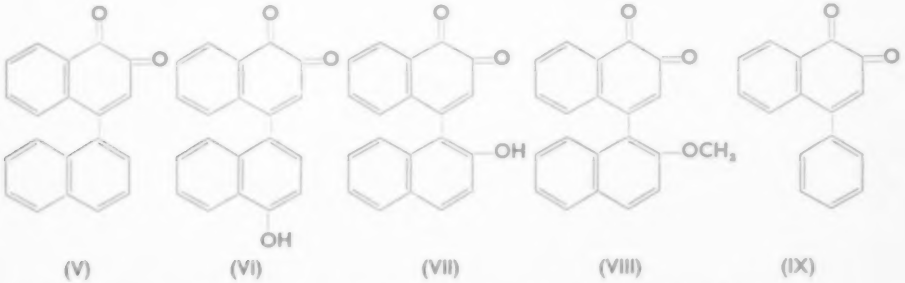
(I) (II) (III)

In letzter Zeit sind auch optisch aktive Isatine dargestellt worden, die eine deutlich auswählende stereochemische Spezifität gegenüber D- und L-Aminosäuren zeigen.[6,8] Es handelt sich um atropisomere Derivate des Diisatyls (IV).



(IV)

Isatin kann als *o*-Chinon des Indols betrachtet werden. Es ist deshalb nicht überraschend, dass auch carbocyclische *o*-Chinone eine Dehydrasewirkung gegenüber Aminosäuren ausüben.[11-15] Allerdings liegt ihr Redoxpotential so, dass nur Sauerstoff, nicht Methylenblau als Acceptor verwendet werden kann. Anfänglich störte die Eigenschaft mancher *o*-Chinone, schon ohne Substrat leicht autoxydiert zu werden. Später fanden wir aber Derivate des β-Naphthochinons, die nicht mehr autoxydabel und dabei sehr starke Katalysatoren sind.[15] Meist sind es 4-Naphthylnaphthochinone-(1, 2) (V–VIII) während das 4-Phenylderivat (IX) merkwürdigerweise autoxydabel ist.



(V) (VI) (VII) (VIII) (IX)

[11] W. Langenbeck, R. Schaller und K. Arneberg, *Ber. Dtsch. Chem. Ges.* **75**, 1483 (1942).
[12] W. Langenbeck, O. Tarhan, G. Keitel und B. Hirsch, *Chem. Ber.* **81**, 356 (1948).
[13] W. Langenbeck, H. Le Blanc und B. Lukowczyk, *Chem. Ber.* **87**, 496 (1954).
[14] H. Pracejus, *Liebigs Ann.* **601**, 61 (1957).
[15] H. Cassebaum und W. Langenbeck, *Chem. Ber.* **90**, 339 (1957).

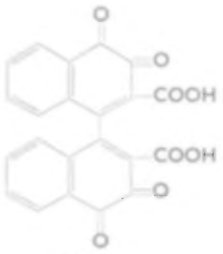
Ebenso wie die Isatinderivate bauen auch die *o*-Chinone Aminosäuren zu Aldehyd, Ammoniak und Kohlendioxyd ab, nicht zu α-Ketosäuren wie die natürlichen Aminosäuren-Dehydrasen.

Auch in der Reihe der *o*-Chinone sind atropisomere, stereochemisch spezifische Derivate hergestelle worden (X, XI). Bei X trat die stereochemische Spezifität nur bei Gegenwart von Hämin zutage, also mit einer kombinierten Hauptvalenz-Chelatkatalyse. Hierbei wird nämlich die zweite Teilreaktion der Hauptvalenzkatalyse

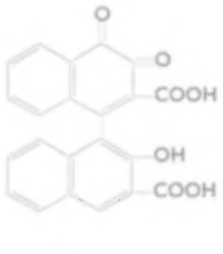
(1) *o*-Chinon + Aminosäure ⟶ *o*-Hydrochinon + Aldehyd + Ammoniak + Kohlendioxyd

(2) *o*-Hydrochinon + Sauerstoff ⟶ *o*-Chinon + Wasserstoffperoxyd

beschleunigt und die erste zur langsamsten. Dies ist für eine stereochemische Spezifität erforderlich, die Umsetzunge des Katalysators mit dem asymmetrischen Substrat muss geschindigkeitsbestimmend sein.



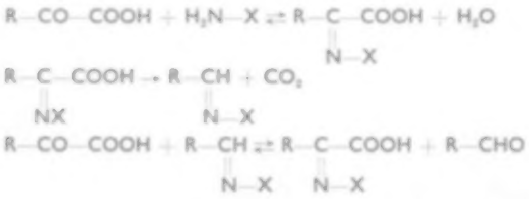
(X)



(XI)

Der zweite von mir nachgewiesene Hauptvalenzkatalysator war der Acetaldehyd.[16] Nach einer alten Arbeit von Liebig hydratisiert er Dicyan zu Oxamid. Ich konnte hochaktive Vinyliminoester als Zwischenstoffe auffinden.

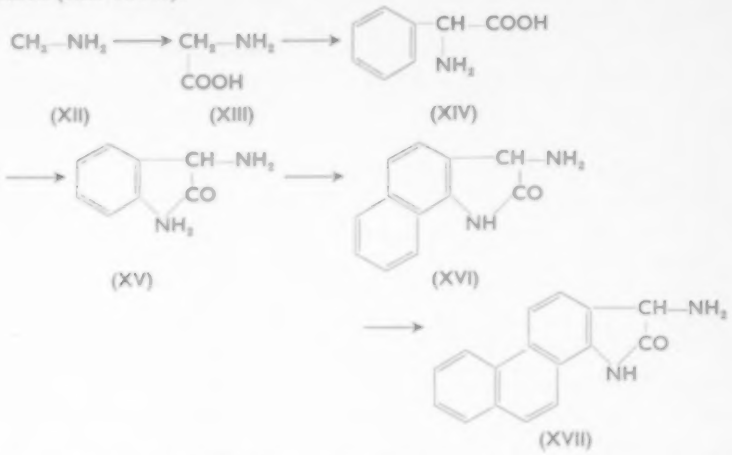
Darauf wurde die Decarboxylierung der α-Ketosäuren bei Gegenwart von primären Aminen entdeckt.[17–22] Sie läuft nach folgendem Cyclus ab:



Da die primär entstehenden Schiffschen Basen sehr wasserempfindlich sind, gelingt die Reaktion nur in nichtwässrigen Lösungsmitteln, am besten in Phenolen. Diese Katalyse ist dadurch besonders interessant, dass eine fünfstufige Aktivierung durch

[16] W. Langenbeck, *Liebigs Ann.* **469**, 16 (1929).
[17] W. Langenbeck und R. Hutschenreuter, *Z. Anorg. Chem.* **188**, 1 (1930).
[18] W. Langenbeck, R. Hutschenreuter und R. Jüttemann, *Liebigs Ann.* **485**, 53 (1931).
[19] W. Langenbeck, R. Jüttemann und F. Hellrung, oxindols, *Liebigs Ann.* **499**, 201 (1932).
[20] W. Langenbeck, F. Hellrung und R. Jüttemann, *Liebigs Ann.* **512**, 276 (1934).
[21] W. Langenbeck und O. Gödde, *Ber. Dtsch. Chem. Ges.* **70**, 669 (1937).
[22] W. Langenbeck und K. Weissenborn, *Ber. Dtsch. Chem. Ges.* **72**, 724 (1939); W. Langenbeck und G. Triem, *Ber. Dtsch. Chem. Ges.* **69**, 248 (1936).

Substitution erzielt werden konnte (mit Phenylglyoxylsäure als Substrat). Sie verläuft über folgende Stufen (XII–XVII):



(XII) (XIII) (XIV) (XV) (XVI) (XVII)

Die Gesamtaktivierung ist etwa 6000-fach. Die Versuche wurden 1939 vorläufig abgeschlossen. Eine Fortsetzung ist nur aussichtsreich, wenn es gelingt, die Reaktion in wässriger Lösung bei Gegenwart von Chelatkatalysatoren auszuführen. Versuche in dieser Richtung sind bereits in Angriff genommen. Schon Metallionen allein, z.B. Magnesium-, Mangan- und Aluminiumionen zersetzen in wässriger Lösung Brenztraubensäure unter Kohlendioxydentwicklung, führen aber zu komplizierten Reaktionsprodukten, die z.T. aufgeklärt werden konnten.[23]

Die von R. Kuhn und Mitarbeitern[24] entdeckte Bildung von Polyenalen aus Crotonaldehyd und Acetaldehyd bei Gegenwart von Piperidinacetat:

$$CH_3{-}CH{=}CH{-}CHO + CH_3{-}CHO \rightarrow CH_3{-}CH{=}CH{-}CH{=}CH{-}CHO + H_2O \text{ usw.}$$

konnte von uns verbessert werden.[25,26] Bisher war es ein Nachteil, dass neben den offenkettigen Polyenalen in grossen Mengen harzige und vor allem auch cyclische Nebenprodukte entstanden. Die Bildung solcher Nebenprodukte liess sich vermeiden, wenn man die Kondensation des Acetaldehyds bei tiefen Temperaturen (−10°) vornahm. Bei dieser Anordnung konnte als Katalysator Dimethylamin mit der doppelten Menge Essigsäure mit Vorteil verwendet werden. Als Nebenprodukte traten dann fast nur noch Crotonaldehyd und Aldol auf. Die Reaktion verläuft wahrscheinlich nach folgendem Mechanismus:

$$CH_3{-}(CH{=}CH)_x{-}CHO + (CH_3)_2\overset{\oplus}{N}H_2 \rightleftarrows CH_3{-}(CH{=}CH)_x{-}CH{=}\overset{\oplus}{N}(CH_3)_2 + H_2O$$

$$\xrightarrow{CH_3{-}CHO} CH_3{-}(CH{=}CH)_x{-}CH{=}CH{-}CHO + (CH_3)_2\overset{\oplus}{N}H_2$$

Sekundäre Amine beschleunigen nicht nur, wie schon Knoevenagel gefunden hatte, die Aldolkondensation und verwandte Reaktionen, sondern sie bewirken auch

[23] A. Schellenberger, *Liebigs Ann.* im Druck.
[24] R. Kuhn und M. Hoffer, *Ber. Dtsch. Chem. Ges.* **63**, 2164 (1930); R. Kuhn, W. Badstübner und C. Grundmann, *Ber. Dtsch. Chem. Ges.* **69**, 98 (1936); R. Kuhn, C. Grundmann und H. Trischmann, *Z. Physiol. Chem.* **248**, IV (1937); R. Kuhn und C. Grundmann, *Ber. Dtsch. Chem. Ges.* **71**, 2274 (1938).
[25] W. Langenbeck, Die Synthese von Poyenaldehyden als Hauptvalenzkatalyse. *X. Int. Congr. Chem., Roma* 16 (1938).
[26] W. Langenbeck, *Synthese von Fettsäuren aus Acetaldehyde* S.35. Chem. Techn. Sonderheft (1952).

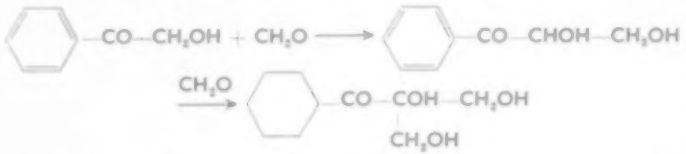
die Anlagerung von Wasser an Crotonaldehyd.[27,28] Es bildet sich ein echtes Gleichgewicht heraus nach der Gleichung:

$$CH_3-CH=CH-CHO + H_2O \rightleftarrows CH_3-CHOH-CH_2-CHO$$

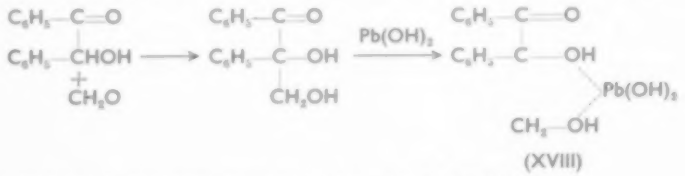
Die Gleichgewichtskonstante in einem Überschuss von Wasser hat etwa den Wert 0,6. Der beste Katalysator ist Sarkosin das sich auch bei den Aldolkondensation bewahnt hat.[29]

Eine sehr interessante katalytische Reaktion ist die Kondensation des Formaldehyds mit sich selbst, wobei zuckerähnliche Oxo-hydroxy-Verbindungen entstehen. Sie wurde schon im Jahre 1861 von Butlerow entdeckt, führte in der Hand von Emil Fischer zu einheitlichen Zucker-osazonen und wurde später von Löw durch Anwendung von Bleihydroxyd (statt Kalziumhydroxyd) als anorganischem Hilfskatalysator verbessert. Schmalfuss konnte zeigen, dass die Reaktion durch Zusatz ihrer Reaktionsprodukte beschleunigt wird, dass also eine Autokatalyse vorliegt. Unsere Untersuchungen[30-35] haben diese Feststellung auf kinetischem Wege bestätigt. Darüber hinaus konnten organische Katalysatoren gefunden werden, die noch weit wirksamer sind als die Reaktionsprodukte, sodass bei Zusatz solcher Stoffe der autokatalytische Charakter der Reaktion verschwindet und in einen echten katalytischen Verlauf übergeht.

Die wirksamsten Katalysatoren sind Benzoylcarbinol und seine Derivate. Es liess sich nachweisen, dass mit Formaldehyd bei Gegenwart von Bleihydroxyd oder Bleioxyd definierte Hauptvalenz-Zwischenstoffe entstehen:



Die Wirkung der zugesetzten Metallhydroxyde hängt stark von der Natur der Kationen ab. Natriumhydroxyd wirkt z.B. sehr schlecht. Dagegen ist Bleihydroxyd bei Gegenwart von organischen Katalysatoren sogar noch in schwach saurer Lösung aktiv. Daraus muss man schliessen, dass die Formaldehydkondensation eine kombinierte Hauptvalenz-Chelatkatalyse ist. Es war, geschichtlich betrachtet, die erste Kombination dieser Art. Am Modell des Benzoins konnten wir die Bildung von Chelaten nachweisen, die vielleicht folgende Konstitution besitzen (XVIII):

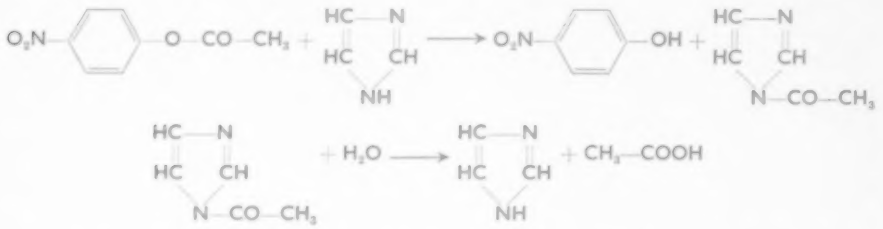


(XVIII)

[27] W. Langenbeck und R. Sauerbier, *Ber. Dtsch. Chem. Ges.* **70**, 1540 (1937).
[28] W. Langenbeck und R. Grochalski, *Z. Phys. Chem.* **197**, 191 (1951).
[29] W. Langenbeck und G. Borth, *Ber. Dtsch. Chem. Ges.* **75**, 951 (1942).
[30] W. Langenbeck, *Naturwissenschaften* **30**, 30 (1942).
[31] S. Hünig, *Biochem. Z.* **313**, 31 (1942).
[32] E. Katzschmann, *Ber. Dtsch. Chem. Ges.* **77**, 579 (1944).
[33] W. Langenbeck, W. Sander, F. Kühn, S. Hünig und E. Katzschmann, *Angew. Chem.* **61**, 186 (1949).
[34] W. Langenbeck, *Neue Untersuchungen über die Formaldehydkondensation* S.119. Vontragstagung 1953 der Chemischen Gesellschaft in der DDR.
[35] W. Langenbeck, K. H. Krüger, K. Schwarzer und J. Welker, *J. Prakt. Chem.* **3**, 196 (1956).

Das Gemisch der Reaktionsprodukte wurde katalytisch hydriert und die dabei entstandenen mehrwertigen Alkohole fraktioniert destilliert. Dabei zeigte es sich, dass durch den Zusatz der organischen Katalysatoren die Ausbeute an niederen Kondensationsprodukten (Glykolaldehyd, Dioxyaceton usw.) vermehrt wird. Auch heterogene organische Katalysatoren auf der Basis von Austauscherharzen konnten entwickelt werden. Sie haben den Vorteil, dass sie nach beendeter Reaktion leicht von dem Reaktionsgemisch getrennt und wieder verwendet werden können.

Auf dem Gebiet der Hauptvalenzkatalysatoren mit Hydrolasewirkung waren bisher nur sehr geringe Erfolge erzielt worden.[36–43] Erst in jüngster Zeit haben amerikanische Autoren die Beobachtung gemacht, dass die Hydrolyse des *p*-Nitro-phenylacetats durch Imidazol und einige seiner Derivate beschleunigt wird,[44] und wir konnten zeigen, dass dabei 1-Acetyl-imidazol als isolierbarer Zwischenstoff auftritt.[45] Es spielt sich also mindestens zum Teil folgende Hauptvalenzkatalyse ab:



Durch diese Ergebnisse ist im Bereich der organischen Katalyse ein neues Arbeitsgebiet erschlossen worden, das noch viele Möglichkeiten verspricht. Besonders die Kombination von Imidazolderivaten mit Chelatkatalysatoren erscheint aussichtsreich.

Chelatkatalysatoren

Chelatkatalysen sind in unserem Sinne nur solche Reaktionen, deren Katalysatoren bereits Chelate sind. Die zahlreichen Fälle, bei denen freie Metallionen dadurch katalytische wirken, dass sie mit ihren Substraten komplexe Bindungen eingehen, gehören nicht in unser Arbeitsgebiet. Chelatkatalysatoren sind also Chelate mit katalytischer Wirkung.

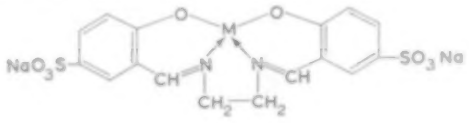
Unsere Untersuchungen über Chelatkatalysatoren knüpfen an eine ältere Arbeit von R. Kuhn und A. Wassermann[46] an, aus der hervorgeht, dass die Eisen(II)-Chelate des Dipyridyls und Phenanthrolins im Entstehungszustande besonders lebhaft Wasserstoffperoxyd zersetzen. Die Autoren nahmen an, dass bei der Bildung der Eisen(II)-Chelate aus Eisen(III)-salz, Wasserstoffperoxyd und Dipyridyl zunächst

[36] W. Langenbeck und J. Baltes, *Ber. Dtsch. Chem. Ges.* **67**, 387 (1934).
[37] W. Langenbeck und J. Baltes, *Ber. Dtsch. Chem. Ges.* **67**,1204 (1934).
[38] W. Langenbeck und F. Baehren, *Ber. Dtsch. Chem. Ges.* **69**, 514 (1936).
[39] W. Langenbeck und K. Hölscher, *Ber. Dtsch. Chem. Ges.* **72**, 724 (1939).
[40] W. Langenbeck, *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten* (2. Aufl.) S.78. Springer-Verlag, Berlin, Göttingen und Heidelberg (1949).
[41] H. Mix und W. Langenbeck, *Ergebn. Enzymforsch.***13**, 207–299 (1954).
[42] W. Langenbeck, *Z. Elektrochem.* **54**, 193 (1950).
[43] W. Langenbeck, *Advanc. Enzymol.* **14**, 163, 173 (1953).
[44] T. C. Bruice und G. L. Schmir, *Arch. Biochem. Biophys.* **63**, 484 (1956); *J. Amer. Chem. Soc.* **79**, 1663 (1957); M. L. Bender und B. W. Turnquest, *Ibid.* **79**, 1652 (1957).
[45] W. Langenbeck und R. Mahrwald, *Chem. Ber.* **90**, 2423 (1957).
[46] R. Kuhn und A. Wassermann, *Liebigs Ann.* **503**, 203 (1933).

Chelate mit einer Koordinationslücke entstehen, die besonders aktiv sind. Die experimentellen Ergebnisse von Kuhn und Wassermann konnten wir auch an Phenanthrolinderivaten bestätigen.[47]

Solche ungesättigten Chelate halten sich natürlich nur kurze Zeit, sie gehen bald in die gesättigten Chelate mit geringerer katalytischer Wirkung über. Wir stellten nun beständige Chelate mit Koordinationslücke dadurch her, dass wir Liganden benutzten, deren "Zähnigkeit" die Koordinationszahl des Metallions nicht erreichte. Die so entstehenden Koordinationslücken werden zwar wahrscheinlich von dem Lösungsmittel ausgefüllt, dieses wird aber so locker gebunden, dass es leicht von dem Substrat verdrängt werden kann. Denn hierauf scheint es anzukommen: Das Substrat muss sich, um katalytisch verändert zu werden, an das Chelat komplex anlagern. Für solche Gedankengänge gab es schon in dem natürlichen Hämin ein Vorbild, das ja auch ein ungesättigtes Chelat von erheblicher katalytischer Wirkung ist (s.u.).

Vierzähnige Liganden sind die früher von P. Pfeiffer untersuchten Schiffschen Basen des Salicylaldehyds mit Äthylendiamin. Ihre Chelate sind meist in Wasser schwer löslich und daher für katalytische Versuche weniger geeignet. Wir haben deshalb die leicht löslichen Chelate der Schiffschen Base des Äthylendiamins mit Salicylaldehyd-sulfonsäure [Sulfosalicylaldehydäthylendiimin (XIX)] zu katalytischen Versuchen herangezogen.[48]



XIX

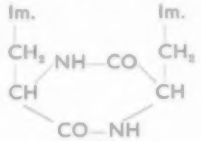
Gemessen wurde die Oxydation von Pyrogallol zu Purpurogallin durch Wasserstoffperoxyd (Peroxydasewirkung) und die Zersetzung des Wasserstoffperoxyds zu Sauerstoff und Wasser (Katalasewirkung). Das Ergebnis war sehr überraschend. Das Kobaltchelat von (XIX) war peroxydatisch 10,000 mal so aktiv wie die freien Kobaltionen. Das Kobaltchelat des ähnlich wie (XIX) gebauten Pyridoxalphosphatäthylendiimins, das sich also von einem natürlichen Coferment ableitet, hatte die 1000 fache Wirkung der Kobaltionen. Katalatisch waren besonders die Mangan(II)-chelate sehr aktiv.

Zu den Chelaten mit Koordinationslücke gehören auch das Hämin und das Hämoglobin. Die katalytische Aktivität des roten Blutfarbstoffes ist schon sehr lange bekannt, und zwar jetzt fast genau 100 Jahre. 1857 beobachtete C. F. Schönbein, dass Guajaktinktur bei Gegenwart von Wasserstoffperoxyd und roten Blutkörperchen eine blaue Farbe annahm. Die katalytischen Fähigkeiten des Hämins wurden 1926 von R. Kuhn[49] entdeckt. 1932 konnten wir zeigen, dass Imidazol und manche seiner Derivate eine besonders hohe Affinität zum Hämin besitzen, und dass diese "Imidazol-parahämatine" auch katalytisch besonders aktiv sind.[50,51,52] Dabei sind es wahrscheinlich nicht die koordinativ abgesättigten Verbindungen (Hämin.

[47] W. Langenbeck und F. Kasper, *Chem. Ber.* **89**, 2460 (1956).
[48] W. Langenbeck und K. Oehler, *Chem. Ber.* **89**, 2455 (1956).
[49] R. Kuhn und L. Brann, *Ber. Dtsch. Chem. Ges.* **59**, 2370 (1926).
[50] W. Langenbeck, R. Hutschenreuter und W. Rottig, *Ber. Dtsch. Chem. Ges.* **65**, 1750 (1932)
[51] W. Langenbeck und S. Fittkau, *Chem. Ber.* **87**, 501 (1954).
[52] W. Langenbeck, *S. B. Dtsch. Akad. Wiss.* Nr. 3 (1957).

2 Imidazol) welche katalysieren, sondern die Verbindungen mit Koordinationslücke (Hämin. Imidazol). Auch im Hämoglobin sind nur 5 Koordinationsstellen des Eisens besetzt. Die sechste wird im Oxyhämoglobin vom molekularen Sauerstoff in Anspruch genommen. Dieser wird aber leicht vom Substrat verdrängt, da er nur locker gebunden ist. Daher sind auch die Oxyhämoglobine katalytisch hochaktiv. Der Globinanteil der Blutfarbstoffe, der ja bei jeder Tierart verschieden ist, übt einen deutlichen Einfluss auf den Grad der katalytischen Aktivität aus. Wir konnten z.B. zeigen, dass das Oxyhämoglobin des Meerschweinchens eine dreimal so starke Peroxydase ist wie das Hunde-Oxyhämoglobin.[50,51]

Chelatkatalysen beschränken sich in der lebenden Zelle nicht nur auf die Häminfermente (Katalase, Peroxydase und Atmungsfermente), sondern wir wissen heute, dass auch sehr viele Apofermente Metallionen nach Art der Chelate gebunden enthalten. Wir haben deshalb damit begonnen zu untersuchen, wie die katalytische Aktivität von Metallionen durch Aminosäuren, Peptide und cyclische Peptide verändert wird.[53,54,55] Dabei zeigte sich, dass Arginin die katalatische Aktivität des Kupferions stark erhöht, die des Cobaltions aber hemmt. Offenbar bilden sich mit Kupfer ungesättigte, mit Cobalt gesättigte Chelate. Auch Histidinanhydrid (XX):



(XX)

als Vertreter der cyclischen Peptide aktiviert das Kupferion.[54] Wir halten es durchaus für möglich, dass in Apofermenten cyclische Peptide gebunden vorkommen, mit spezifischen komplexbildenden Gruppen (Imidazol, Guanidin, Thiol usw.).

Eine besondere Klasse von Chelatkatalysatoren sind die Salze von organischen Sulfonsäuren. Nachdem Losowoi[56] die Beschleunigung der Veresterung von Carbonsäuren durch anorganische Salze gefunden hatte und Hanske[57] zeigen konnte, dass diese Wirkung auch von der Natur der Anionen abhängt, haben wir die Wirkung von Salzen organischer Sulfonsäuren auf die Veresterung gemessen.[58,59] Dabei zeigte sich, dass auch die in wässriger Lösung fast neutral reagierenden Salze, wie das Kalzium- und Magnesiumsalz der Benzolsulfonsäure, in methanolisch-essigsaurer Lösung eine starke Erhöhung der Wasserstoffionen-Konzentration bewirken. Wir müssen deshalb annehmen, dass sich in methanolischer Lösung aus sulfonsaurem Salz und Essigsäure starke komplexe Säuren bilden, etwa nach folgendem Schema (XXI),

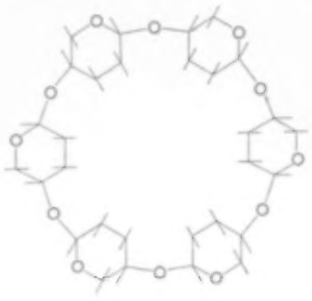
(XXI)

deren Wasserstoffionen die Veresterung beschleunigen.

[53] H. Mix, W. Tittelbach-Helmrich und W. Langenbeck, *Chem. Ber.* **89**, 69 (1956).
[54] H. Mix, *Naturwissenschaften* **43**, 469 (1956).
[55] W. Langenbeck, H. Mix und W. Tittelbach-Helmrich, *Chem. Ber.* **90**, 2699 (1957).
[56] A. W. Losowoi, *Zh. obsch. khim.* **2**, 65 (1932); C.1933, I, 1731.
[57] W. Hanske, *Z. Anorg. Chem.* **266**, 216 (1951).
[58] W. Langenbeck und R. Mahrwald, *Liebigs Ann.* **605**, 111 (1957).
[59] W. Langenbeck und R. Mahrwald, *Liebigs Ann.* **611**, 1 (1958).

Einschlusskatalysatoren

F. Cramer[60] beobachtete, dass die ringförmig gebauten Schardingerschen Cyclodextrane (z.B. XXII) die Reaktionsfähigkeit mancher eingeschlossenen Stoffe erhöhen. So nimmt die Autoxydationsgeschwindigkeit des Furoins bei Gegenwart der Cyclodextrane zu. Cramer nimmt an, dass im Innern der Cyclodextranringe ein stärker



XXII

alkalisches Milieu vorhanden ist, als in der Lösung. Auch an der Amylose, die ja eine spiralige Struktur besitzt, konnte ich in noch unveröffentlichten Versuchen mit R. Koch schwache katalytische Wirkungen nachweisen.

W. Lautsch hat sich in zahlreichen Arbeiten um das Problem der kombinierten Chelat-Einschlusskatalysen bemüht.[61] Er konnte zeigen, dass die katalytischen Wirkungen des Hämins durch angefügte Polypeptidketten erhöht werden.

Basische Katalysatoren

Bei den basischen Katalysatoren spielt ihre organisch-chemische Natur keine besondere Rolle. Anorganische Basen können ebensogut oder besser wirken. Bemerkenswert sind aber die Erscheinungen der stereochemischen Spezifität, die man mit optisch aktiven Basen, z.B. Alkaloiden hervorrufen kann. Die ersten Versuche auf diesem Gebiete stammen von Bredig und Fajans.[62] D- und L-Camphocarbonsäure (XXIII) wurden durch Chinin mit verschiedener Geschwindigkeit zu Campher und Kohlendioxyd zersetzt.

XXIII

Beziehungen zwischen Konstitution und Wirkung

Das Problem, Beziehungen zwischen Konstitution und Aktivität bei organischen Katalysatoren zu finden, ist ein Teilproblem zu der Frage nach Konstitution und Reaktionsgeschwindigkeit von organischen Stoffen überhaupt. Bekanntlich sind solche Probleme heute noch nicht exakt und zahlenmässig lösbar, wenn sich auch

[60] F. Cramer, *Chem. Ber.* **86**, 1576 (1953); *Angew. Chem.* **68**, 118 (1956).
[61] W. Lautsch, *Angew. Chem.* **66**, 123 (1954), und spätere Arbeiten.
[62] G. Bredig und K. Fajans, *Ber. Dtsch. Chem. Ges.* **41**, 752 (1908).

aus der Elektronentheorie der organischen Bindung manche qualitativen Ansätze ergeben haben. Im Wesentlichen ist man auch heute noch auf ein empirisches Durchprobieren einer möglichst grossen Zahl neu synthetisierter Stoffe angewiesen, wobei sich aber die Erfolgsquote durch einige systematische Richtinien sehr verbessern lässt.

Bei den Hauptvalenzkatalysatoren haben sich folgende drei Regeln für die Aktivierung stets bewährt:

(1) Jede Hauptvalenzkatalyse besteht aus mindestens zwei Teilreaktionen. Es ist nicht erforderlich, beide gleichzeizig zu aktivieren, sondern es genügt, wenn man die Teilreaktion mit der kleinsten Geschwindigkeitskonstante durch Einführung aktivierender Gruppen beschleunigt.

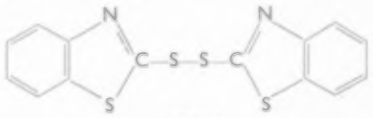
(2) Die Wirkung mehrerer aktivierender Gruppen multipliziert sich. So ist es möglich, die günstigste Kombination von aktivierenden Gruppen dadurch zu finden, dass man nacheinander die aktivierenden Gruppen einführt und jeweils die aktivsten Derivate aussucht.

(3) Die aktivierenden Gruppen dürfen von der aktiven Gruppe nicht durch längere gesättigte aliphatische Ketten getrennt sein, wohl aber durch aromatische Kerne oder Doppelbindungen.

Bei den Chelatkatalysatoren wird nun vielleicht das Prinzip der koordinativ ungesättigten Chelate für die Auffindung neuer Katalysatoren von Nutzen werden. Dagegen wissen wir noch nichts über den Einfluss von aktivierenden Gruppen und Doppelbindungen, von der Natur der komplexbildenden Gruppen und dem Redoxpotential der Chelate. Bei den Einschlusskatalysatoren reicht das experimentelle Material überhaupt noch nicht aus, um allgemeine Regeln aufzustellen. während man bei basischen Katalysatoren mit einer Abhängigkeit der Aktivität von der Basenstärke rechnen kann (Brönstedt).

Technische Probleme

Eine grössere industrielle Bedeutung haben unter den organischen Katalysatoren bisher nur die organischen Vulkanisationsbeschleuniger erlangt. Wir konnten auf thermoanalytischem Wege nachweisen, dass das Di-benzothiazol-disulfid (XXIV)



(XXIV)

mit elementarem Schwefel Zwischenstoffe eingeht,[63,64] die vielleicht den Charakter von organischen Polysulfiden besitzen. Der technische Vorteil der organischen Vulkanisationsbeschleuniger beruht u.a. darauf, dass sie billig sind und daher nicht wiedergewonnen zu werden brauchen, was beim Prozess der Vulkanisation ja sowieso unmöglich wäre. Bei zukünftigen technischen Anwendungen von organischen Katalysatoren wird man aber darauf bedacht sein müssen, sie in eine heterogene Form zu bringen, sodass man sie leicht von der Reaktionslösung abfiltrieren kann. Ein gangbarer Weg dazu besteht in der Verknüpfung mit Austauscherharzen, die durch ihre Quellbarkeit dem Lösungsmittel und den Substraten einen Zugang gestatten.

[63] W. Langenbeck und H. C. Rhiem, *Ber. Dtsch. Chem. Ges.* **68**, 2304 (1935).
[64] W. Langenbeck, *Kautschuk* **12**, 156 (1936).

Dieser Weg ist bei den organischen Katalysatoren der Formaldehydkondensation schon mit Erfolg beschritten worden.[34] Da sich die Kondensationsprodukte zu mehrwertigen Alkoholen vom Glykol und Glycerin bis zu den sechswertigen Alkoholen hydrieren lassen, könnte dem Verfahren eine technische Bedeutung zukommen.

Beziehungen zu den Fermenten

Die bisher isolierten und aufgeklärten Cofermente (Cocarboxylase, Lactoflavinphosphat, Pyridoxalphosphat,[65] DPN und Coferment A) haben sich sämtlich als Hauptvalenzkatalysatoren erwiesen. Bei der Cocarboxylase wurde die von uns vorausgesagte primäre Aminogruppe durch die spätere Konstitutionsaufklärung bestätigt. Auch die gleichzeitige Acyloinbildung bei der Wirkung der α-Ketosäurendecarboxylase kam schon unseren Modellen zu.

Die Wirkung der Glyoxalase mit Ihrem Coferment Glutathion konnte von V. Franzen und von Th. Wieland[66] schon mit einfachen Mercaptanen modellmässig nachgeahmt werden. Dabei bilden sich Zwischenstoffe nach Art von Halbacetalen, sodass kein Zweifel bestehen kann, dass auch die Coglyoxalase ein Hauptvalenzkatalysator ist.

Da man in Apofermenten häufig charakteristische Metallionen gefunden hat, wird man viele Apofermente als Chelatkatalysatoren betrachten müssen. Eine grosse Zahl von Fermentreaktionen stellen sich somit als kombinierte Chelat-Hauptvalenzkatalysen dar. Nach unserer Anschauung werden in solchen Fällen die Substrate an die Cofermente zu Zwischenstoffen gebunden, während die Cofermente ihrerseits von den Apofermenten gebunden und aktiviert werden. Alle Cofermente besitzen Atomgruppen, welche sie zur Komplexbildung geeignet machen. Die bekannte Erscheinung, dass Fermentreaktionen häufig durch einen Überschuss des Substrates gehemmt werden (z.B. bei der Carboxylase), würde sich danach so erklären, dass das Coferment durch das Substrat vom Apoferment abgedrängt wird.

Die moderne Biochemie hat uns gelehrt, über welche Zwischenprodukte die Reaktionen der lebenden Zelle ablaufen. Die Chemie der organischen Katalysatoren schliesst sich an diese Ergebnisse unmittelbar an. Sie will u.a. zeigen, welchen Mechanismus die Einzelreaktionen unter Mitwirkung der Fermente besitzen. Die analytische Untersuchung der Fermente allein kann das nicht leisten, weil der Mechanismus durch die Kompliziertheit der Fermentstruktur verdeckt wird. Es ist eine allgemeine Erscheinung, dass Gesetzmässigkeiten am besten an einfachen Modellen erkannt werden können.

[65] D. E. Metzler, M. Ikawa und E. E. Snell, *J. Amer. Chem. Soc.* **76**, 648 (1954).
[66] V. Franzen, *Chem. Ber.* **88**, 1361 (1951); *Angew. Chem.* **68**, 381 (1956); Th. Wieland und F. Jaenicke, *Chem. Ber.* **88**, 641, 1967 (1955).

Tetrahedron, 1958, Vol. 3, pp. 197–208. Pergamon Press Ltd., London

REACTIONS OF NON-ACTIVATED ARYL HALIDES WITH NUCLEOPHILIC AGENTS INDUCED BY ALKALI AMIDES IN LIQUID AMMONIA*

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Abstract—It has been shown that the reactions of nucleophiles with non-activated aryl halides, discovered by Bergstrom to be induced by alkali amides in liquid ammonia, proceed by way of a benzyne-type intermediate. The ease with which a given nucleophile can compete with amide ion does not appear to be a simple function of either its basic strength or nucleophilic character as measured in other reactions. Thus, the anions of a number of weak acids line up qualitatively in competitive power as follows: fluorenyl anion ~ anilide > thiophenolate ~ triphenylmethide > acetophenone enolate anion ~ phenylacetylide > phenolate > pyrrolate > alkoxides, iodide or cyanide. The results indicate benzyne to be a highly unstable entity.

IN 1936 Bergstrom and co-workers[1,2] reported that chlorobenzene, bromobenzene and iodobenzene react with sodium or potassium amide in liquid ammonia solution at −33° to give approximately 50 per cent of aniline, along with smaller amounts of diphenylamine, triphenylamine and *p*-aminobiphenyl. They also observed that potassium anilide and potassium diphenylamide under the same conditions failed to react with chlorobenzene and bromobenzene, unless potassium amide was added. Potassium diphenylmethide and potassium triphenylmethide reacted very slowly with chlorobenzene in liquid ammonia solution at −33°; however, slow addition of potassium amide caused a marked increase in the reaction rate. The products were triphenylmethane and tetraphenylmethane, respectively. Potassium diphenylmethide was found to catalyze the reaction of potassium diphenylamide with chlorobenzene, possibly owing to the formation of amide ion through the following equilibrium:

$$(C_6H_5)_2CHK + NH_3 \rightleftharpoons (C_6H_5)_2CH_2 + KNH_2$$

Since potassium diphenylmethide ($pK_a = 34$)[3] is a weaker base than potassium amide ($pK_a = 36$)[3], the equilibrium would be expected to lie far on the left.

Bergstrom and co-workers[4,5,6] have reported that quinaldine, lepidine, α-picoline, *o*-tolunitrile, acetonitrile and fluorene can be phenylated with chlorobenzene and bromobenzene in the presence of potassium amide in liquid ammonia as follows:

$$RCH_3 \xrightarrow[C_6H_5X]{KNH_2} RCH_2(C_6H_5) + RCH(C_6H_5)_2 + RC(C_6H_5)_3$$

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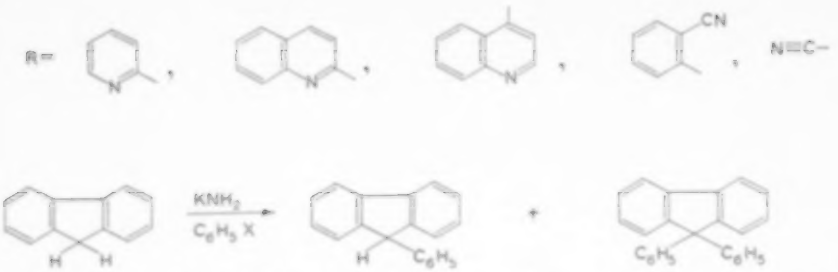
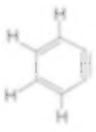
† Contribution No. 2241, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.

[1] F. S. Bergstrom, R. E. Wright, C. Chandler and W. Gilkey, *J. Org. Chem.* **1**, 170 (1936).
[2] R. E. Wright and F. W. Bergstrom, *J. Org. Chem.* **1**, 179 (1936).
[3] J. B. Conant and G. W. Wheland, *J. Amer. Chem. Soc.* **54**, 1212 (1932).
[4] R. A. Seibert and F. W. Bergstrom, *J. Org. Chem.* **10**, 544 (1945).
[5] F. W. Bergstrom and R. Agostinho, *J. Amer. Chem. Soc.* **67**, 2152 (1945).
[6] P. H. Dirstine and F. W. Bergstrom, *J. Org. Chem.* **11**, 55 (1946).



Recently Leake and Levine[7] have shown that ketones can be similarly phenylated in liquid ammonia with the aid of potassium amide.

In all the above-mentioned reactions, aniline, diphenylamine and triphenylamine are formed as side-products. The formation of the various products can be easily rationalized on the assumption that the metallic amides dehydrohalogenate the aryl halide molecules with the formation of benzyne (I), which is then attacked by the various nucleophilic agents present in competition with amide ions. The purpose of this research was to establish whether the elimination–addition mechanism is involved



I

and, if so, to determine whether nucleophilicity or base strength determines the ease of attack of a given species on the benzyne intermediate.

In determining whether the reaction between aryl halides with nucleophilic agents with potassium amide in liquid ammonia proceeds through a benzyne intermediate, advantage was taken of the fact that substitutions by the elimination–addition mechanism invariably lead to rearrangement with tolyl halides or with isotopically labeled phenyl halides. The reaction between potassium triphenylmethide and chlorobenzene[1-^{14}C] was first considered, since, if a way could be found to degrade the resulting isotopically labeled tetraphenylmethane to triphenylacetic acid, it would be possible to determine whether the reaction proceeded with rearrangement or by direct substitution. However, no successful degradation scheme was found for conversion of tetraphenylmethane to triphenylacetic acid.

The reaction between sodium phenylacetylide and aryl halides was investigated next. Diphenylacetylene was obtained in 26 per cent yield from the reaction of sodium phenylacetylide with bromobenzene. When *p*-bromotoluene was substituted for bromobenzene, the reaction product contained, besides small amounts of 3- and 4-methyldiphenylacetylenes, large amounts of diaryl- and triaryl-amines. Attempts to determine the ratio of the two acetylenes by oxidative degradation to a mixture of benzoic and toluic acids did not lead to satisfactory results, for it was found that the oxidation did not proceed quantitatively. Finally the phenyltolylacetylenes were separated from the other products by elution with hexane through an alumina column and analyzed by means of infrared spectroscopy. The reaction between sodium

[7] W. Leake and R. Levine, *Chem. & Ind. (Rev.)* **37**, 1160 (1955).

phenylacetylide and *o*-bromotoluene was investigated in a similar way. In both cases, the reaction appeared to proceed through a benzyne intermediate, the isomer ratios of the phenyltolylacetylenes agreeing rather closely with the isomer ratios obtained in the amination of the corresponding halotoluenes.[8,9] The results are summarized in Table 1.

In order to see whether nucleophilicity or base strength determines the ease of attack of an anion on benzyne, bromobenzene was treated with a variety of nucleophilic agents in the presence of potassium amide in liquid ammonia. The conditions and yields are summarized in Table 2. For the various nucleophiles, the relative yields of substitution products are considered to provide a rough measure of the competitive powers of the nucleophiles relative to amide ion. The complexity of the reactions makes more accurate measurements of competition factors difficult. The

TABLE 1. ORIENTATION IN THE REACTION OF HALOTOLUENES WITH PHENYLACETYLIDE AND AMIDE IONS

Isomer	X	$Y^{\ominus}$	*Ortho* (per cent)	*Meta* (per cent)	*Para* (per cent)
p	Br	$C_6H_5C{\equiv}C^{\ominus}$	0	57	43
	Cl	$NH_2^{\ominus}$ [a]	0	62	48
o	Br	$C_6H_5C{\equiv}C^{\ominus}$	49	51	0
	Br	$NH_2^{\ominus}$ [a]	48·5	51·5	0

[a] Data from Roberts *et al.*[8]

data of Table 2 clearly prove that, on the whole, benzyne shows a considerable lack of selectivity in its addition reactions. This is consonant with a high degree of exothermicity[9] in such additions, as would be expected from the substantial angle strain of (I).

It is evident from the data of Table 2 that the base strength is not the sole determining factor in the attack of a nucleophilic species on benzyne, for triphenylmethane, aniline, fluorene, acetophenone and thiophenol, whose pK_a values range from 33 to 8·4, give rather comparable yields of products. Similarly, it is not possible directly to correlate nucleophilicity with ease of attack on benzyne, for while nucleophilicity decreases in the following order:[10] $C_6H_5S^- > I^- > CN^- > (CH_3)_3CO^- > C_6H_5O^-$, the ease of attack on benzyne appears to decrease in the following order: $C_6H_5S^- > C_6H_5O^- > I^-, CN^-, (CH_3)_3CO^-$.

The nucleophilic order mentioned above for various anions was determined with

[9] Further indication that rather different nucleophiles may attack benzyne-type intermediates to give similar product ratios is provided by the results of Huisgen *et al.* [cf. *Angew. Chem.* **69**, 389 (1957)], on the reactions which proceed by an elimination–addition mechanism of 1-halonaphthalenes with organolithium compounds and the lithium salts of secondary amines. In each case 1- and 2-substituted naphthalenes were formed in approximately equal ratios, despite the marked differences in the character of the addends.

[8] J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, *J. Amer. Chem. Soc.* **78**, 611 (1956).

[9] G. S. Hammond, *J. Amer. Chem. Soc.* **77**, 334 (1955).

[10] A. Streitwieser, Jr., *Chem. Rev.* **56**, 571 (1956).

aliphatic halides as substrates, and, since the transition state for attack of an anion on benzyne is almost certainly different in nature from the transition state in S_N2 reactions, it is perhaps not surprising that the order of reactivity is different. An additional complication is possibly provided by the differences in solvent used in the benzyne-type reactions and those employed in determining the nucleophilicities toward alkyl halides.

Of very considerable significance is the fact that amide ions and alkoxide ions appear to be much less effective competitors relative to the rather less powerfully basic, but unsaturated, phenolate, pyrrolate and thiophenolate ions than might reasonably be expected. Amide and alkoxide ions are relatively small anions with

TABLE 2. REACTION OF STRONG BASES AND NUCLEOPHILIC AGENTS WITH BROMOBENZENE

$$C_6H_5Br + R^{\ominus} \xrightarrow[NH_3]{NH_2^{\ominus}} C_6H_5R + Br^{\ominus}$$

R—H	pK_a	Reaction time (hr)	Mole ratio RH/C_6H_5Br	Yield (per cent)
Ammonia*	36	—	0·7–1·5	56
Triphenylmethane	33	4·25	0·33	39
Aniline†	27	—	—	57
Fluorene	25	5·0	0·5	58‡
Phenylacetylene	21	0·75	4·0	26
Acetophenone§	19	—	—	28
tert.-Butyl alcohol	18	0·75	2·0	0
Pyrrole	16·5	3·0	1·6	~1
Phenol	10·0	2·5	1·0	~4
Thiophenol	8·4	3·5	1·0	42
Hydrogen cyanide	9·1	4·0	1·8	0
Hydrogen iodide	<0	8·0	6·2	0

* Data from Bergstrom *et al.*[1]
† Data from Wright and Bergstrom.[3]
‡ Combined yield of 9-phenyl- and 9,9-diphenylfluorene.
§ Data from Leake and Levine.[7]

concentrated charges presumably rather tightly solvated by ammonia molecules. The unsaturated anionic nucleophiles may be more reactive toward benzyne, because their relatively dispersed charges are more loosely solvated by ammonia molecules at the reactive site, thus reducing the degree of steric hindrance to attack on benzyne. In order that a factor of this sort dominant over the effects usually important in nucleophilic substitution, it is necessary that activation energies for addition to benzyne be small.[9]

EXPERIMENTAL

General procedure for reactions of nucleophilic agents with aromatic halides in the presence of alkali amides in liquid ammonia

The apparatus used for the reaction of various nucleophilic agents with aromatic halides in the presence of alkali amides in liquid ammonia was similar to that used by Schlatter[11] for the preparation of *cyclo*propyl cyanide. A 1 l. three-necked

[11] M. J. Schlatter, *J. Amer. Chem. Soc.* **63**, 1733 (1941).

flask was fitted with a ball-and-socket sealed mechanical stirrer, a condenser containing solid carbon dioxide, and a tube extending to the bottom of the flask. A second 2 l. three-necked flask was fitted with a ball-and-socket sealed mechanical stirrer, a short inlet tube and a condenser containing solid carbon dioxide connected to a drying tower. The condenser attached to the 1 l. flask was connected by means of rubber tubing to a T-tube, through which flowed a very gentle stream of dry nitrogen.

After the apparatus had been thoroughly dried by flashing with a Bunsen burner and flushing with dry nitrogen, the two condensers were filled with acetone–solid carbon dioxide mixture, and the required amounts of liquid ammonia were condensed in the two flasks. Traces of water in the liquid ammonia were removed by adding small amounts of sodium or potassium metal until the blue color in the solution persisted for at least 1 min. Sodium or potassium amide was prepared in both flasks through the reaction of the required amounts of alkali metals with liquid ammonia in the presence of a small amount of anhydrous ferric chloride. The appropriate active hydrogen compound was added to the 2 l. flask and 15–30 min were allowed for the establishment of the following equilibrium, which in most cases was far to the right:

$$RH + MNH_2 \rightleftharpoons RM + NH_3$$

The aryl halide was then added to the 2 l. flask and the tubes attached to the two flasks were connected by means of rubber tubing. The alkali amide solution (or slurry, in the case of sodium amide) was forced slowly in small amounts from the 1 l. flask into the 2 l. flask by momentarily closing the outlet tube of the nitrogen stream. In a few cases, a Fisher Electric Hosecock, operated by a solenoid timer, was advantageously employed. After all the amide had been added, the reaction mixture was set aside for various periods of time, and then the unreacted bases were decomposed by careful addition of an excess of ammonium chloride or water. The reaction flask was opened to the atmosphere and the liquid ammonia was allowed to evaporate overnight. The residue was mixed with an organic solvent and water, and the products were isolated as described below.

Tetraphenylmethane

Potassium amide (0·46 mole) in 500 ml of liquid ammonia was added during 4½ hr to a solution of potassium triphenylmethide (0·10 mole) and bromobenzene (0·30 mole) in 500 ml of liquid ammonia. The reaction mixture was set aside for 30 min, then an excess of ammonium chloride was added and the solvent was allowed to evaporate. The solid residue was taken up in hot benzene and water. The organic layer was washed several times with dilute mineral acid and water and then filtered. The solvent was evaporated; the residue was washed several times with small amounts of ether and recrystallized from benzene. The yield of tetraphenylmethane, m.p. 282·5–283·5°, was 10·0 g (31 per cent).

Diphenylacetylene

Sodium amide (0·62 mole) in 500 ml of liquid ammonia was added during 45 min to a solution of sodium phenylacetylide (0·93 mole) and bromobenzene (0·62 mole) in 500 ml of liquid ammonia. The reaction mixture was set aside for 30 min, an excess of ammonium chloride was added and the solvent was allowed to evaporate. The residue was dissolved in ether and water; the organic layer was washed several

times with dilute hydrochloric acid and water. The ether was evaporated, and the unreacted phenylacetylene and bromobenzene were removed by distillation under reduced pressure.

The residue was dissolved in low-boiling light petroleum (boiling range 30–60°); a small amount of an insoluble blue material was removed by filtration, and the solution was passed through a column packed with 250 g of acid-washed alumina which had been activated by being heated for 30 min to a dull red color in a nitrogen atmosphere. Diphenylacetylene (11·0 g, 26 per cent), m.p. 51–60°, was obtained by evaporation of the eluate. The product was identified by comparison of its infrared and ultraviolet spectra with those of an authentic sample.

Attempts to prepare anisylphenylacetylenes and trifluoromethyldiphenylacetylenes through the reactions of *o*-bromoanisole and *o*-chlorotrifluoromethylbenzene led only to undistillable tarry materials.

Reaction of p-*bromotoluene with sodium phenylacetylide in the presence of potassium amide in liquid ammonia*

Potassium amide (0·38 mole) in 300 ml of liquid ammonia was slowly added during 1½ hr to 1 l. of liquid ammonia containing 0·72 mole of sodium phenylacetylide and 0·26 mole of distilled *p*-bromotoluene. After all the potassium amide had been added, the mixture was set aside for 30 min and then treated with an excess of ammonium chloride, and the solvent was allowed to evaporate overnight. The solid residue was dissolved in dilute hydrochloric acid and pentane. The organic layer was washed several times with dilute hydrochloric acid and water, then it was dried over anhydrous magnesium sulfate and the solvent was evaporated on a steam bath. The residue was distilled through a semimicro column[12] to 40° (2 mm) to remove phenylacetylene and *p*-bromotoluene.

Since preliminary experiments had shown that the diarylamines present in the product could not be removed either by distillation through a 100 cm spinning-band column or by extraction with concentrated mineral acid, the residue after the distillation was eluted with hexane through a 3·4 × 30 cm column packed with acid-washed alumina that had been activated by being heated at 125° for 12 hr *in vacuo*. 3-Methyl- and 4-methyl-diphenylacetylene were eluted completely with 3 l. of solvent. A succeeding 1 l. fraction contained no high-boiling residue. The solvent was evaporated; an infrared spectrum of the residue showed the presence of only 3- and 4-methyldiphenylacetylene contaminated with a small amount of *p*-bromotoluene. The product was again eluted with 1 l. of carbon tetrachloride through a 2 × 20 cm column packed with alumina that had been activated by the above-mentioned method to remove some silicon grease that contaminated the product. After the carbon tetrachloride had been removed by evaporation, 7·8 g (16 per cent) of a mixture of 3- and 4-methyldiphenylacetylenes containing some *p*-bromotoluene was obtained. This mixture was analyzed by using a Perkin–Elmer (Model 21) Infrared Spectrophotometer at 12·28, 12·48 and 12·85 μ with the aid of calibration graphs constructed from the absorptions of the pure constituents at each wavelength. Cells 0·1 mm thick were used and the solvent was carbon disulfide. Known mixtures were found to be analyzable to ± 2 per cent and showed no change in composition when passed through an alumina column in hexane solution. The reaction mixture was found to

[12] C. W. Gould, Jr., G. Holzmann and C. Niemann, *Analyt. Chem.* **20**, 361 (1948).

contain 3- and 4-methyldiphenylacetylenes in the ratio of 57 to 43 and 15 per cent of *p*-bromotoluene.

Preparation of authentic samples of 3- and 4-methyldiphenylacetylenes will be described below.

Reaction of o-*bromotoluene with sodium phenylacetylide in the presence of potassium amide in liquid ammonia*

The reaction of *o*-bromotoluene with sodium phenylacetylide in the presence of potassium amide in liquid ammonia was carried out as with the *p*-isomer.

The crude product, after the starting materials had been removed by distillation, was eluted with hexane through a column containing 300 g of activated alumina. Both 2- and 3-methyldiphenylacetylene were completely eluted with 2 l. of solvent. An infrared analysis showed that small amounts of *o*-bromotoluene and aliphatic hydrocarbons (probably from impurities in the hexane) were present along with the two acetylenes.

An elemental analysis showed that the bromine content of the mixture was 1·65 per cent, which corresponds to 3·5 per cent of *o*-bromotoluene.

A carbon disulfide solution of the mixture, containing 42·9 mg of the mixture per g of solution, was analyzed by infrared spectroscopic procedures with the aid of a calibration curve for 3-methyldiphenylacetylene at 12·85 μ and found to contain 19·8 mg of 3-methyldiphenylacetylene (46 per cent of the mixture). Since none of the other components absorbed in the region of the spectrum used to determine the concentration of this compound, the error in the analysis was probably no more than 2 per cent. No direct determination of 2-methyldiphenylacetylene could be made, since no suitable peak was found in the infrared spectrum.

The infrared absorption of the three methyldiphenylacetylenes are practically identical in the 3·0–3·7 μ region of the infrared spectrum. The amount of aliphatic hydrocarbons present in the mixture was estimated roughly by spectroscopic analysis of solutions of 3-methyldiphenylacetylene and hexane in carbon disulfide in different proportions and at different concentrations. When the 3-methyldiphenylacetylene to hexane ratio was 95 to 5, the spectra of the above mixture and the mixture obtained from the reaction of *o*-bromotoluene and phenylacetylene matched very closely. The amount of 2-methyldiphenylacetylene present in the mixture was then obtained by difference. The composition (by weight) was estimated to be: 46 per cent of 3-methyldiphenylacetylene, 45 per cent of 2-methyldiphenylacetylene, 4 per cent of *o*-bromotoluene and 5 per cent of aliphatic hydrocarbons. The ratio of 3- to 2-methyldiphenylacetylene was 51 to 49.

2-*Methyl-*, 3-*methyl-* and 4-*methylstilbenes*

4-Methylstilbene was prepared by the method of Meerwein *et al.*[13] From 70 g (0·65 mole) of *p*-toluidine and 90 g (0·61 mole) of cinnamic acid there was obtained, after one recrystallization from ethanol, 33·0 g (24 per cent) of 4-methylstilbene; m.p. 118–120·5° (m.p. 119·5° [14]).

3-Methylstilbene was prepared by the same method in 17 per cent yield; after two recrystallizations from methanol, the m.p. was 40–45° (m.p. 48° [14]).

[13] H. Meerwein, E. Büchner and J. van Emster, *J. Prakt. Chem.* **152,** 237 (1939).
[14] F. Bergman and D. Shapiro, *J. Org. Chem.* **12,** 57 (1949).

2-Methylstilbene was prepared by the same method in 5 per cent yield; b.p. 125–140° (1 mm) [b.p. 125° (0·15 mm [14])].

2-Methyl-, 3-methyl- and 4-methyldibromostilbenes

4-Methyldibromostilbene was prepared by the method described in *Organic Syntheses*.[15] From 33 g (0·17 mole) of 4-methylstilbene was obtained 35 g of crude product, m.p. 184–187°. Upon evaporation of the mother liquors, 1·0 g of additional product, m.p. 194–196·5°, was obtained. The yield of pure 4-methyldibromostilbene was 31·0 g (51·5 per cent); m.p. 199–200° (m.p. 188° [14]). Since the m.p. of the product was appreciably different from the one reported in the literature, the product was submitted for elemental analysis. *Anal.* Calcd. for $C_{15}H_{14}Br_2$: C, 50·88; H, 3·98; Br, 45·14. Found: C, 50·78; H, 4·05; Br, 45·16.

3-Methyldibromostilbene was prepared by the same method in 70 per cent yield; m.p. 182–183°. *Anal.* Calcd. for $C_{15}H_{14}Br_2$: C, 50·88; H, 3·98; Br, 45·14. Found: C, 51·00; H, 4·04; Br, 45·12.

2-Methyldibromostilbene was prepared by the same method in 55 per cent yield; m.p. 159–161° (m.p. 159°[14]).

2-Methyl-, 3-methyl- and 4-methyldiphenylacetylene

4-Methyldiphenylacetylene was prepared by the general method described in *Organic Syntheses*.[15] From 31 g (0·0865 mole) of 4-methyldibromostilbene was obtained 16 g (96 per cent) of 4-methyldiphenylacetylene, m.p. 71·5–72·5°. After one sublimation *in vacuo*, the m.p. of the product was raised to 72·5–73·5°. *Anal.* Calcd. for $C_{15}H_{14}$: C, 93·71; H, 6·29. Found: C, 93·74; H, 6·23.

3-Methyldiphenylacetylene was prepared by the same method in 76·5 per cent yield from 3-methyldibromostilbene; b.p. 126–128° (2 mm), m.p. 30–31°. *Anal.* Calcd. for $C_{15}H_{12}$: C, 93·71; H, 6·29. Found: C, 93·78; H, 6·25.

2-Methyldiphenylacetylene was prepared by the same method in 92 per cent yield from 2-methyldibromostilbene; b.p. 120–122° (2 mm). The product was further purified by elution with hexane through a column packed with acid-washed alumina and very slow distillation at 70° in a short-path distillation apparatus. *Anal.* Calcd. for $C_{15}H_{12}$: C, 93·71; H, 6·29. Found: C, 93·58; H, 6·43.

Reaction of potassium pyrrolate with bromobenzene in the presence of potassium amide in liquid ammonia

Potassium amide (0·45 mole) in 500 ml of liquid ammonia was added during 3 hr to a solution containing 0·5 mole of potassium pyrrolate and 0·311 mole of bromobenzene in 600 ml of liquid ammonia. The solvent was allowed to evaporate slowly, so that the total volume of solution was kept approximately constant.

The reaction mixture, after all the potassium amide had been added, was set aside for 45 min, and then an excess of ammonium chloride was added, followed by 500 ml of ether. After the solvents had evaporated, the residue was dissolved in ether and water; the organic layer was washed five times with dilute hydrochloric acid and twice with distilled water. The ether was evaporated and the residue distilled through a semimicro column.[13] One gram of distillate, b.p. 64–70° (1 mm), was collected. This material solidified upon standing; m.p. 53–58°. After a sublimation

[15] *Organic Syntheses* Coll. Vol. III, p. 350. John Wiley, New York (1955).

and three recrystallizations from 70 per cent ethanol, the m.p. was raised to 59–60°. The infrared and ultraviolet spectra were identical with those of N-phenylpyrrole; and the m.p. of the product showed no depression when mixed with an authentic sample of N-phenylpyrrole.[16] The yield of crude N-phenylpyrrole was 1·0 g (1·4 per cent).

Reaction of 9-fluorenylpotassium with bromobenzene in the presence of potassium amide in liquid ammonia

Potassium amide (0·53 mole) in liquid ammonia was added during 5 hr to a solution of 9-fluorenylpotassium (0·229 mole) and bromobenzene (0·45 mole) in 200 ml of ether and 500 ml of liquid ammonia. The reaction mixture was set aside for 15 min, an excess of ammonium chloride was added, and the solvents were allowed to evaporate. The residue was dissolved in benzene and water; the organic layer was washed several times with dilute hydrochloric acid and water, and then the solvent was evaporated.

9-Phenylfluorene is soluble in 95 per cent ethanol to the extent of less than 50 mg/100 ml, while 9,9-diphenylfluorene is practically insoluble in the same solvent, so the crude reaction product was digested with 100 ml of 95 per cent ethanol, cooled and washed with 100 ml of 95 per cent ethanol to separate diphenylamine and triphenylamine as well as much of the excess of fluorene. The treatment was then repeated with two 500 ml portions of 95 per cent ethanol. The residual alcohol-

TABLE 3. ANALYSIS OF A MIXTURE OF FLUORENE, 9-PHENYLFLUORENE AND 9,9-DIPHENYLFLUORENE

Compound	Concentration (mg/l.)	Absorption (optical-density units)			Amount present in the unknown mixture (mg/l.)
		301·5 mμ	305·0 mμ	310·0 mμ	
Fluorene	231	1·35	0·45	0·03	30
9-Phenylfluorene	378	0·62	1·37	0·14	218
9,9-Diphenylfluorene	464	0·53	0·45	1·13	127
Reaction mixture	375	0·68	0·97	0·40	

insoluble product weighed 39·3 g. The strong band at 2·95 μ of diphenylamine was absent from the infrared spectrum of the product and there was an absorption minimum at 297 mμ in the ultraviolet spectrum where triphenylamine shows strong absorption.

The mixture was analyzed with the aid of its ultraviolet spectrum in benzene solution by using 1·00 mm cells in a Cary Recording Spectrophotometer (Model 11 M). The results of this analysis are summarized in Table 3. The yield of 9-phenylfluorene was 22·3 ± 1·5 g (40 per cent) and the yield of 9,9-diphenylfluorene was 13·8 ± 0·8 g (18 per cent).

A sample weighing 2·9 g was fractionally sublimed *in vacuo*. A fraction of 1·40 g, which sublimed at a bath temperature of 80–130°, was recrystallized twice from ethanol; its m.p. was 148·5–149·0°. The ultraviolet spectrum of this compound was identical with that of 9-phenylfluorene. The m.p. showed no depression when

[16] C. H. F. Allen, M. R. Gilbert and D. M. Young, *J. Org. Chem.* **2**, 230 (1937).

mixed with an authentic sample[17] of the above compound. A final fraction of 0·95 g, which sublimed at 135–170°, showed m.p. of 222–224°, after two recrystallizations from benzene. The m.p. was not depressed when the substance was mixed with an authentic sample of 9,9-diphenylfluorene.[18] The ultraviolet spectrum was identical with that of 9,9-diphenylfluorene.

Reaction of potassium thiophenolate with bromobenzene in the presence of potassium amide in liquid ammonia

Potassium amide (0·44 mole) in 250 ml of liquid ammonia was added during 3·5 hr to a solution of potassium thiophenolate (0·34 mole) and bromobenzene (0·346 mole) in 700 ml of liquid ammonia. An excess of ammonium chloride was then added and the solvent was allowed to evaporate. The residue was dissolved in water and ether; the organic layer was washed first with dilute hydrochloric acid, then with sodium hydroxide solution and finally with water. It was dried over anhydrous magnesium sulfate; the ether was evaporated and the residue was distilled from a distilling flask. The results of this distillation at a pressure of 3 mm were as follows:

Fraction	1	2	3	4
Temperature (°C)	120–128	128–136	136–144	144–164
Weight (g)	7·9	10·4	11·5	11·6

The ultraviolet spectra of the first three fractions showed them to consist mostly of diphenyl sulfide; the infrared spectra showed the presence of diphenylamine. The infrared and ultraviolet spectra of fraction 4 were similar to the corresponding spectra of pure diphenyl disulfide.

The first three fractions were combined and found by combustion analysis to contain 16·79% sulfur and 0·55% nitrogen. From these data, the combined first three fractions were calculated to consist of 89% diphenyl sulfide, 5% diphenyl disulfide and 6% diphenylamine. The total amount of diphenyl sulfide present was 26 g (0·14 mole, 41 per cent).

A small amount of the combined first three fractions was oxidized at room temperature with 30% hydrogen peroxide in acetic acid. The resulting product melted at 125°, and showed no m.p. depression when mixed with an authentic sample of diphenyl sulfone. Its infrared and ultraviolet spectra were also identical with those of diphenyl sulfone.

Fraction 4 was found to contain 21·1% sulfur as compared to 29·4% calculated for pure diphenyl disulfide, and may have contained some diphenyl sulfide. This fraction solidified partially after a few days in a refrigerator. The supernatant liquid was removed by filtration; 8 g of a slightly yellow solid, m.p. 50–56°, was obtained. After two recrystallizations from ethanol, the m.p. of the solid was raised to 60°; no m.p. depression was observed when the solid was mixed with an authentic sample of diphenyl disulfide. Its infrared and ultraviolet spectra were identical with those of diphenyl disulfide. Presumably, the disulfide arises from oxidation of excess of thiophenolate in the isolation procedures.

[17] F. Ullmann and R. von Wusteinberger, *Ber. Dtsch. Chem. Ges.* **37**, 73 (1904).
[18] W. E. Bachmann, *J. Amer. Chem. Soc.* **55**, 2135 (1933).

Reaction of potassium phenolate with bromobenzene in the presence of potassium amide in liquid ammonia

Potassium amide (0·64 mole) in 500 ml of liquid ammonia was added to a mixture of 0·5 mole of potassium phenolate and 0·51 mole of bromobenzene in 500 ml of liquid ammonia during 2·5 hr. The solution was set aside for 1 hr, and then the unreacted amides were carefully hydrolyzed with 20 ml of water. Water (750 ml) was added, and the mixture was extracted with two 300 ml portions of benzene. The combined extracts were washed successively with 500 ml of 2% sodium hydroxide, two 500 ml portions of 2% hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulfate and distilled through a semimicro column.[12] The amount of bromobenzene recovered was 15 g (0·095 mole).

The fraction (3·8 g) of b.p. 76–108° (2 mm) was shown to contain diphenylamine and diphenyl ether by its ultraviolet and infrared spectra. A ferric chloride test was positive, indicating the presence of some phenol. The mixture was analyzed by means of its ultraviolet spectrum in 95% ethanol and shown to contain about 78% diphenyl ether, 14% diphenylamine and 7% phenol (by difference). The yield of diphenyl ether was 3·0 g (3·5 per cent or 4·2 per cent based on unrecovered bromobenzene).

Part of the product (1·2 g) was dissolved in anhydrous ether and treated with anhydrous hydrogen chloride. Diphenylamine hydrochloride was removed by filtration; the filtrate was washed with a dilute sodium hydroxide solution to remove the phenol present and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was nitrated by the method of Matsumara.[19] The resulting 4-nitrodiphenyl ether, after four recrystallizations from acetic acid, showed m.p. 194–196°, 195–197° [19].

Attempted reaction of potassium tert.*-butoxide with bromobenzene in the presence of potassium amide in liquid ammonia*

A suspension of sodium amide (0·6 mole) in 250 ml of liquid ammonia was added during 45 min to a solution of potassium *tert.*-butoxide (1·2 mole) and bromobenzene (0·6 mole) in 750 ml of liquid ammonia. The solution was set aside for 1 hr, the unreacted bases were decomposed by dropwise addition of water and the solvent was allowed to evaporate. The residue was dissolved in ice-cold water and ether; the organic layer was washed three times with an ice-cold solution of 0·5% hydrochloric acid and then with a solution of potassium carbonate. The basic water extract was treated with bromine water, but no precipitate formed.

The ether layer was washed with cold water, dried over anhydrous magnesium sulfate and distilled. Seventeen grams of bromobenzene was recovered. The product that distilled next was diphenylamine. No *tert.*-butyl phenyl ether was detected.

Attempted reaction of sodium cyanide with bromobenzene in the presence of sodium amide in liquid ammonia

Anhydrous sodium cyanide (0·81 mole) and 0·45 mole of bromobenzene were added to 700 ml of liquid ammonia. A suspension of 0·652 mole of sodium amide in liquid ammonia was added in small portions during 4 hr. The unreacted sodium amide was neutralized with an excess of ammonium chloride. The solvent was evaporated with a stream of nitrogen and the residue was extracted with ether and water.

[19] K. Matsumara, *J. Amer. Chem. Soc.* **52,** 3199 (1932).

The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated and the residue was distilled through a semimicro column.[12] Bromobenzene, aniline, diphenylamine and triphenylamine were collected. The distillation was interrupted because the distillate solidified in the condenser. The residue (7·0 g) was heated under reflux with 100 ml of ethanol containing 10·0 g of potassium hydroxide for 60 hr. The solution was evaporated to dryness under reduced pressure. The residue was dissolved in water, extracted with ether, acidified and again extracted with ether. Evaporation of the ethereal solution gave less than 10 mg of a yellow oil.

Attempted reaction of potassium iodide with bromobenzene in the presence of potassium amide in liquid ammonia

A solution of 0·436 moles of potassium amide in 500 ml of liquid ammonia was added during 8 hr to a solution of 450 g (2·71 mole) of anhydrous potassium iodide and 79 g (0·5 mole) of bromobenzene. The total volume of solution in the reaction flask was maintained constant by allowing the solvent to evaporate slowly. The unreacted base was neutralized with an excess of ammonium chloride, the solvent was evaporated and the residue was extracted with water and ether. The organic layer was washed several times with dilute mineral acid and water, dried over anhydrous magnesium sulfate and distilled through a semimicro column.[12] Bromobenzene (33·5 g), b.p. 51° (18–19 mm), $n_D^{20} = 1{\cdot}5592$, was collected. An infrared spectrum of this fraction showed the total absence of all the bands characteristic of iodobenzene. The next appreciable fraction was diphenylamine.

Tetrahedron, 1958, Vol. 3, pp. 209–224. Pergamon Press Ltd., London

ASYMMETRIC TRIAZINES—XIII

REACTION OF PHOSPHORUS PENTACHLORIDE WITH 4-NITROSOPYRAZOLES

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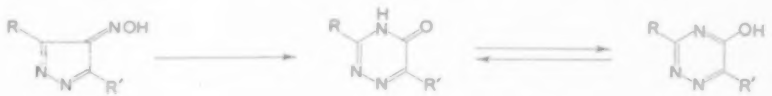
Abstract—The reaction of phosphorus pentachloride with some 3:5-disubstituted-4-nitrosopyrazoles (dimethyl, diphenyl, methyl phenyl and phenyl carbomethoxy) has been investigated. Formation of a new class of compounds, 1-chloro-4-cyano-2:3-diazabuta-1:3-dienes, is described. By treatment with ammonia and subsequent alkali-induced cyclisation these substances are converted into 5-amino-*as*-triazines and reactions of the latter have been investigated.

THE present investigation was undertaken in order to establish if expansion of a pyrazole nucleus to an *as*-triazine ring was feasible by means of a Beckmann rearrangement performed on 4-nitrosopyrazoles unsubstituted at position 1 (III). As it is known these substances, of which only a few examples are described, can be obtained by a general procedure from β-diketones (I) through their *iso*nitroso derivatives (II).

I II III a III b

4-Nitrosopyrazoles are to be considered, owing chiefly to their deep colours, as true nitroso derivatives (IIIa), but a tautomeric *iso*nitroso form (IIIb) is also possible. On the basis of a formal analogy a Beckmann rearrangement operating on 4-nitrosopyrazoles would then afford 5-hydroxy-*as*-triazines (IV). A similar reaction has been



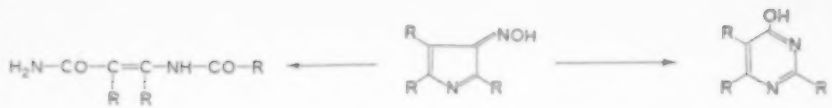
III b IV

reported by Ajello,[1] who allowed phosphorus pentachloride to react with some β-*iso*nitrosopyrroles with substituents at positions 2,4 and 5 (general formula V).

As foreseen, Ajello obtained from (V) the corresponding pyrimidines (VI); however, having observed among the reaction products also open-chain compounds

[*] The results of this investigation have been anticipated in a short communication published in *Mem. Accad. Lincei* **21**, 208 (1956) and presented at the Sixteenth International Congress of Pure and Applied Chemistry, Paris, 17–24 July 1957. Previous papers of this series appeared in *Gazz. Chim. Ital.* **83**, 133 (1953); **84**, 373 (1954); **86**, 484 (1956); **87**, 438 (1957); *Farmaco* **10**, 619 (1955); *R.C. Ist Lombardo* **88**, 173, 185 (1955); **91**, 186 (1957); **91**, 936 (1957).

[1] T. Ajello, *Gazz. Chim. Ital.* **69**, 460 (1939); **70**, 504 (1940); **72**, 325 (1942).



VII V VI

(VII), he inferred the process to be a modification of the true Beckmann rearrangement. Without taking into discussion this reaction mechanism or the origin of products (VII), Ajello's experiments looked encouraging for a new synthesis of the *as*-triazine ring.

The investigation was begun by using 3:5-diphenyl-4-nitrosopyrazole (III, R = R′ = C_6H_5), recently described,[2] prepared by reacting *iso*nitrosodibenzoylmethane (II, R = R′ = C_6H_5) with hydrazine in methanol solution. When a chloroform solution of 3:5-diphenyl-4-nitrosopyrazole was treated with phosphorus pentachloride, the emerald-green characteristic colour of the nitroso compound quickly disappeared with evolution of hydrogen chloride and from the crude reaction product a crystalline yellow solid with empirical formula $C_{15}H_{10}N_3Cl$ was isolated. Alternative structures for this product are 3:6-diphenyl-5-chloro-*as*-triazine (VIII) or the open-chain one corresponding to the chloronitrile (IX).

VIII IX

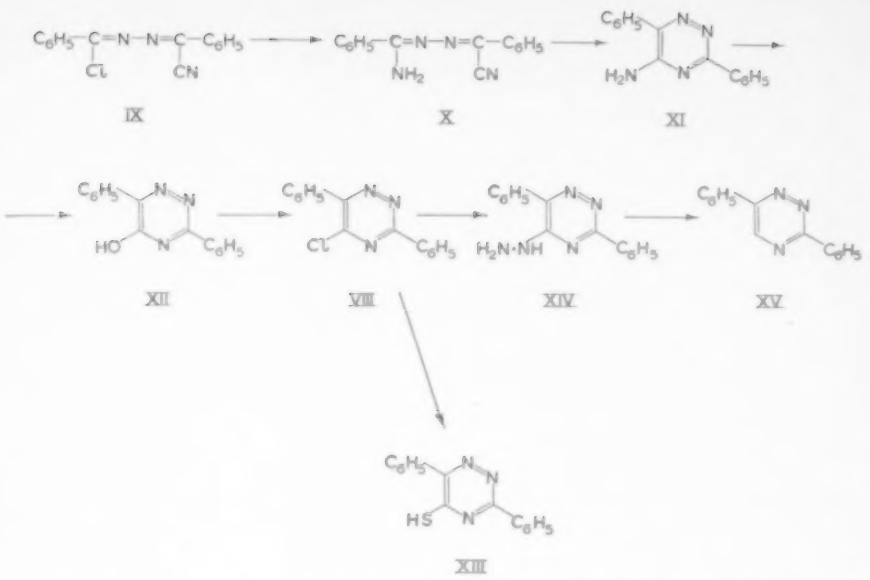
The deep-yellow colour like that observed for $C_{15}H_{10}N_3Cl$ is not easily explained in a cyclic structure such as (VIII). This fact, and chiefly the chemical evidence that will be discussed later, are in favour of the open-chain structure (IX). Compound (IX), presenting rather uncommon structural features, has been related, for its nomenclature, to the corresponding non-nitrogenous system of buta-1:3-diene and consequently identified as 1:4-diphenyl-1-chloro-4-cyano-2:3-diazabuta-1:3-diene.

The formation of the halogenated nitrile (IX) is consistent with results obtained from the so called Beckmann reaction "of the second order".[3] This reaction is typical of those cyclic compounds in which a carbonyl group is contiguous to a ketoximic function.

The halogen atom in (IX) is reactive and can be substituted by an amino group when treated with ammonia in dioxan. The resulting aminonitrile (X) is a yellow coloured crystalline solid, which, when treated with hot strong alkalis, rapidly isomerises to yield a colourless substance. This is a new base, which resists chemical attack, particularly oxidising agents; it forms stable salts with strong mineral acids and even a sparingly soluble permanganate. The formation of this base with simultaneous disappearance of the yellow colour must be interpreted as a cyclisation of the aminonitrile (X) and its structure is therefore that of 3:6-diphenyl-5-amino *as*-triazine (XI).* Ultra-violet and visible region absorption spectra of (X) and (XI) are

* For this and for other *as*-triazine derivatives reported in this work only the "aromatic" structures will be written and no account will be taken of other theoretically possible tautomeric forms.

[2] R. Hüttel, F. Büchele and P. Jochum, *Chem. Ber.* **88**, 1577 (1955).
[3] W. Borsche and W. Sander, *Ber. Dtsch. Chem. Ges.* **47**, 2815 (1914).



shown in Fig. 1. On account of its chemical inertness the amino group in (XI) can be hydrolysed only by prolonged boiling in concentrated hydrobromic acid. In this way 5-hydroxy-3:6-diphenyl-*as*-triazine (XII) is produced as a high-melting colourless solid, soluble in strong alkalis and insoluble in water and most organic solvents.

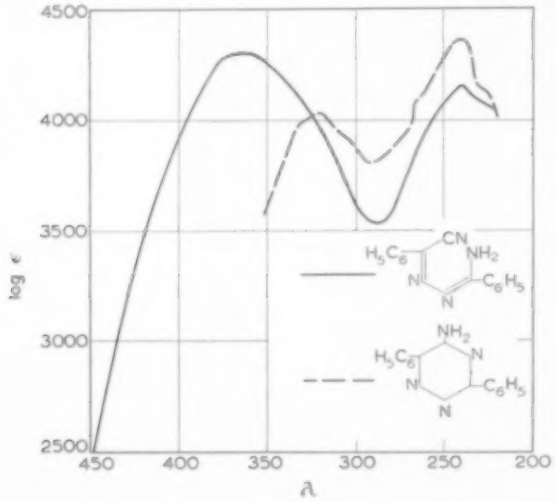


FIG. 1.

5-Hydroxy-3:6-diphenyl-*as*-triazine can be chlorinated by phosphorus pentachloride and the 5-chloro derivative (VIII) on reaction with hydrazine hydrate gives the corresponding 5-hydrazino derivative (XIV).

3:6-Diphenyl-5-chloro-*as*-triazine (VIII) is the cyclic isomer of the chloronitrile (IX) originally produced by the interaction of phosphorus pentachloride and nitrosodiphenyl-pyrazole. As expected, the new substance is colourless and its preparation

indirectly proves the correctness of the open chain structure previously postulated for (IX). Ultra-violet and visible region absorption spectra of the two isomers are shown in Fig. 2.

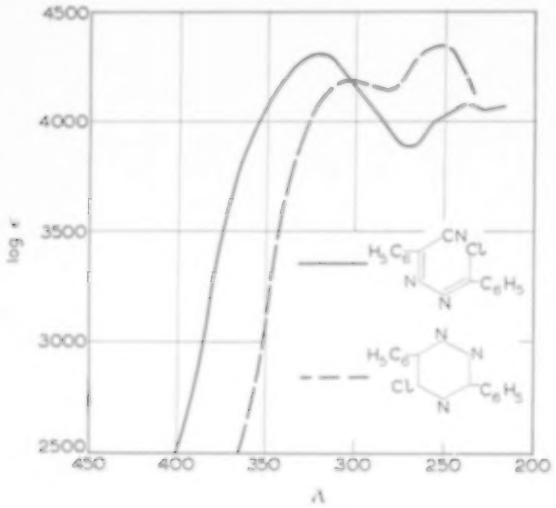


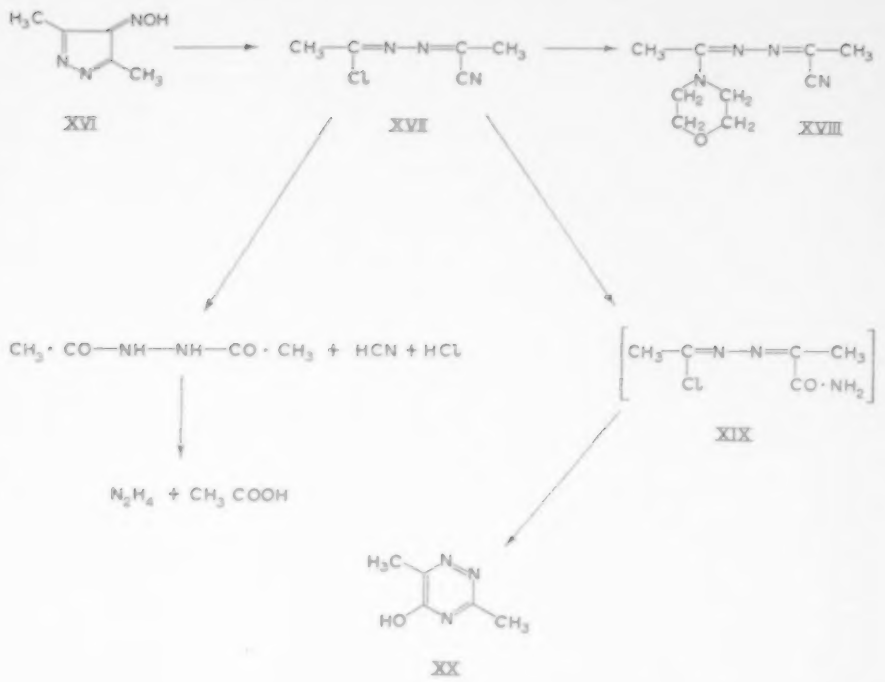
FIG. 2.

5-Hydrazino-3:6-diphenyl-*as*-triazine (XIV) is a high-melting yellow solid, which, unlike the *isomeric* 3-hydrazino-5:6-diphenyl-*as*-triazine, gives no colour reaction in presence of the ferrous ion.[4] Oxidation of (XIV) by yellow mercuric oxide in alcoholic solution by a procedure previously employed in this laboratory[5] yields 3:6-diphenyl-*as*-triazine (XV).

The above series of reactions opens a new sythetic route to the *as*-triazine nucleusn which is only limited by the availability of 4-nitrosopyrazoles. Chlorotriazine (VIII) on treatment with alcoholic sodium hydrosulphide was also transformed into the corresponding 5-thiol derivative (XIII). This substance is the first example of an *as*-triazine with a sulphydryl group at position 5.

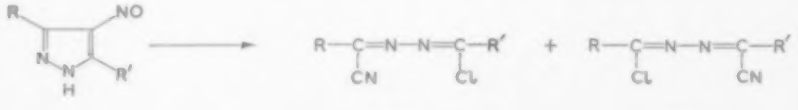
The pyrazole ring cleavage reaction was also applied to 3:5-dimethyl-4-nitroso-pyrazole (III, R = R′ = CH_3 = XVI) prepared in the usual way from acetylacetone (I, R = R′ = CH_3). Phosphorus pentachloride reacts briskly upon dimethyl-nitrosopyrazole (XVI) and the intense blue colour of the nitroso compound immediately disappears. At the same time tarry brown by-products separate, the formation of which can be limited only by employing dimethylnitrosopyrazole of high purity. The main product is a pungent liquid containing chlorine in a highly reactive form. Consistently with the experiment on the diphenyl derivative, this substance has been designated as 2-chloro-5-cyano-3:4-diazahexa-2:4-hexadiene (XVII). Heated with diluted mineral acids (XVII) envolves hydrogen cyanide, while hydrazine and acetic acid can be detected in the solution and further, it reacts smoothly with amines to give bases that are easily purified solids. Morpholine for instance yields base (XVIII),

[4] R. Fusco and R. Trave, *R.C. Ist. Lombardo* **91,** 202 (1957).
[5] S. Rossi, *R.C. Ist. Lombardo* **88,** 187 (1955).



whose structure is confirmed by analytical data. Substance (XVII) undergoes a more complex transformation when exposed to air for a long time. Under these conditions a new colourless sublimable material, m.p. 138°, is slowly formed. This substance, of empirical formula $C_5H_7ON_3$, can be regarded as derived from (XVII) by addition of a molecule of water and loss of hydrogen chloride. Being stable to hydrolytic agents, $C_5H_7ON_3$ does not yield hydrogen cyanide on either acid or alkaline hydrolysis and it cannot be considered as a product derived from simple substitution of chlorine in (XVII) by a hydroxyl group. The new substance is assigned the structure of 3:6-dimethyl-5-hydroxy-*as*-triazine (XX), which could be formed by partial hydrolysis of the nitrile group of (XVII) followed by loss of hydrogen chloride from intermediate amide (XIX). Unfortunately, it has not been possible to extend this investigation owing to poor yields obtained in the dimethylnitrosopyrazole cleavage reaction, to the instability of the resulting chloronitrile and to difficulties in its purification.

It should be noted that up to this point the investigation was carried out on symmetrical nitrosopyrazoles substituted at positions 3 and 5 by identical groups and consequently only one chloro derivative could be obtained. Starting from asymetrically substituted nitrosopyrazoles (III, $R \neq R'$), two isomeric chloronitriles (XXIa and XXIb) could theoretically arise by reaction with phosphorus pentachloride.



In order to investigate this point 4-nitroso-3-phenyl-5-methylpyrazole (XXII), prepared from benzoylacetone (I, R = C_6H_5; R′ = CH_3), was treated with phosphorus pentachloride. The reaction, carried out by the procedure already described gives a chlorine-containing yellow solid with a pungent odour, whose chemical behaviour gives evidence of an open structure and whose chlorine atom reacts quantitatively with silver nitrate in the cold. Derivatives have been obtained by substituting chlorine with nitrogen-containing groups (amino, anilino and morpholine).

On acid hydrolysis substance (XXI) (R = C_6H_5; R′ = CH_3) behaves like the dimethyl derivative (XVII) and forms hydrogen cyanide, hydrogen chloride, benzoic acid, hydrazine and acetic acid, both isomeric structures (XXIa) and (XXIb) (R = C_6H_5; R′ = CH_3) being consistent with such degradation products. Hydrolysis of the morpholine derivative (XXIV) furnishes a clue in favour of structure (XXIb) (R = C_6H_5; R′ = CH_3) as the formation of benzoylmorpholine (XXV) is consistent only with structure (XXIII).

Analogous nitrogen-containing derivatives prepared by reaction with ammonia and and aniline are assigned structures (XXVI) and (XXVII)*. On prolonged exposure to air, compound (XXIII) undergoes a change similar to that observed for the dimethyl derivative (XVII) and yields a new substance with the empirical formula $C_{10}H_9ON_3$. Considering its thermal stability and its resistance to hydrolytic agents, this product is to be assigned structure (XXVIII) of 3-phenyl-6-methyl-5-hydroxy-*as*-triazine. Yields of the product of the cleavage reaction of phosphorus pentachloride on nitrosopyrazole (XXII) and subsequent formation of the triazine compound are lower than those observed for 3:6-diphenylpyrazole. It is to be noted that 3-phenyl-6-methyl-5-hydroxy-*as*-triazine (XXVIII) as well as 3:6-dimethyl-5-hydroxy-*as*-triazine

* Formation of the isomer corresponding to structure (XXIa) (R = C_6H_5; R′ = CH_3) can not be ruled out, and, owing possibly to very poor yields from the cleavage reaction or to its chemical instability, it has not been possible to detect it. Further, one of the structures (XXIa) and (XXIIb) could arise from the *syn* or *anti* configuration of the nitrosopyrazole (IIIb).

(XX) and the triazines of the 3:6-diphenyl series (XI to XV) belong to a new family of *as*-triazines not available through previously known synthetic routes. It has now been shown that the cleavage of the pyrazole ring can be used to obtain *as*-triazines. The preparation of simpler *as*-triazines was undertaken in order to study the chemical behaviour of this heterocyclic structure. For this purpose the action of phosphorus pentachloride on 4-nitrosopyrazoles with substituents in positions 3 and 5 which could be subsequently replaced or eliminated was investigated.

This project was started by synthesising 3-phenyl-5-carbomethoxy-4-nitroso-pyrazole (XXIX).

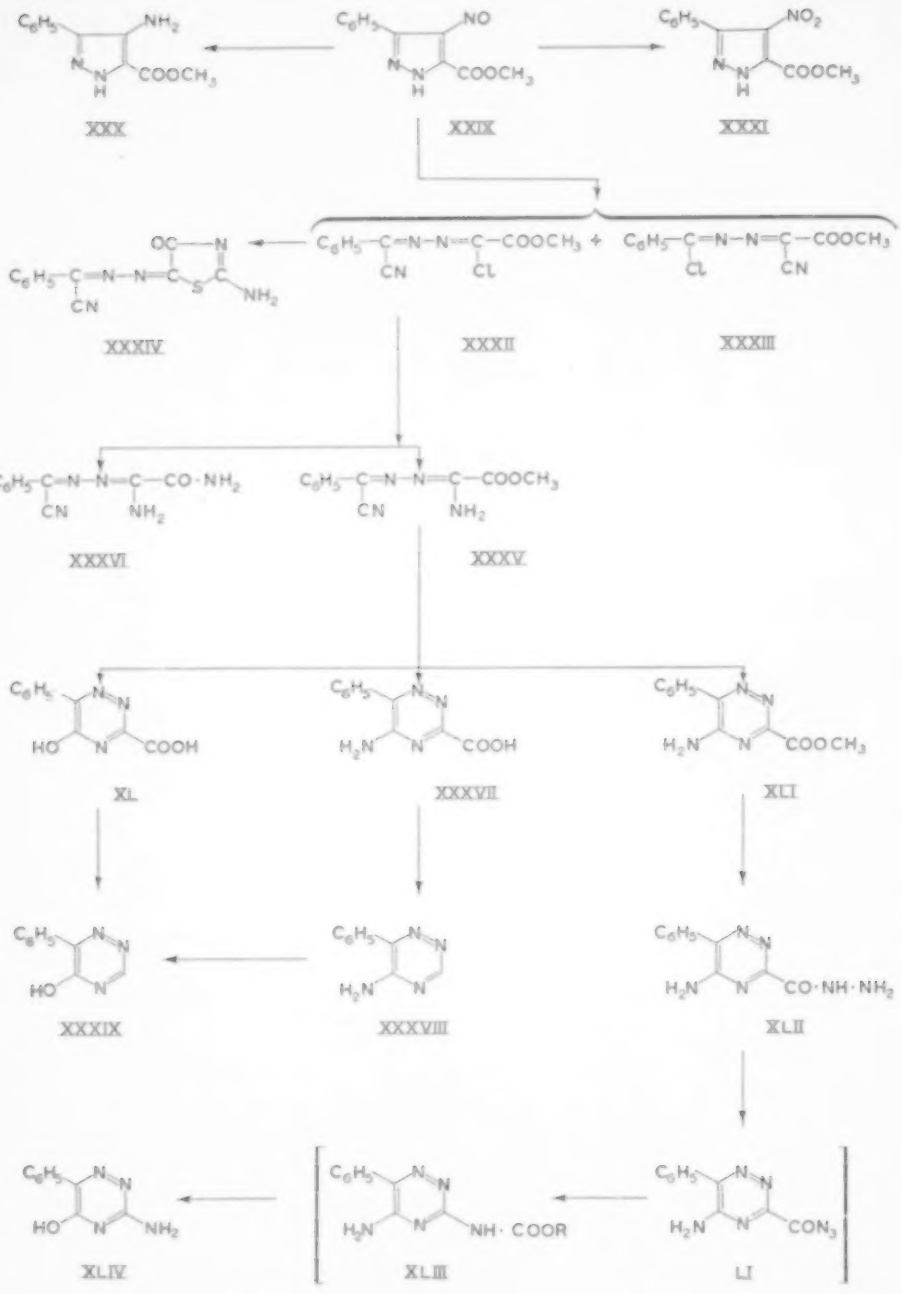
When nitrous acid and hydrazine are allowed to react in rapid succession on methyl acetophenonoxalate (I, R = C_6H_5, R′ = $COOCH_3$) in acetic acid, the solution develops in a short time a characteristic green colour. After dilution in the cold a colourless crystalline solid separates. Satisfactory yields of nitrosopyrazole (XXIX) are obtained only when the intermediate nitrosodiketone (II, R = C_6H_5, R′ = $COOCH_3$) is treated with hydrazine immediately after its formation. Although colourless in the solid state, 3-phenyl-4-nitroso-5-carbomethoxypyrazole (XXIX) shows an intense emerald-green colour when melted or dissolved in organic solvents. This behaviour, which is common to several nitroso compounds, is probably due to the existence in the solid state of a dimeric colourless form. The structure of nitroso-pyrazole (XXIX) has been confirmed through reduction to 3-phenyl-4-amino-5-carbomethoxypyrazole (XXX) and oxidation to 3-phenyl-4-nitro-5-carbomethoxy-pyrazole (XXXI).

With phosphorus pentachloride in chloroform nitrosopyrazole (XXIX) affords a crystalline material, the melting point indicating it to be a mixture of the two isomers, 1-phenyl-1-cyano-4-chloro-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXII) and 1-phenyl-1-chloro-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXIII). The isomers can be separated by fractional crystallisation from benzene and (XXXII), containing an α-chlorocarbomethoxyl group, reacts quantitatively with thiourea to yield a sparingly soluble thiazole derivative (XXIV), which was isolated and analysed. By means of this very sensitive test purification of the higher-melting less-soluble isomer (XXXII) can be controlled.

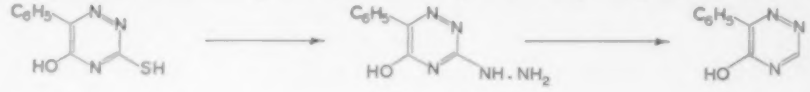
The lower-melting isomer (XXXIII) is obtained in less pure condition. By reaction with ammonia 1-cyano-1-phenyl-4-chloro-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXII) gives the corresponding aminonitrile (XXXV) in 90 per cent yields. With higher temperatures or prolonged contact of gaseous ammonia with the chloro-nitrile the amino amide (XXXVI) is produced. After treatment with potassium carbonate solution amino ester (XXXV) cyclises with simultaneous hydrolysis of the carbomethoxyl group and 5-amino-6-phenyl-*as*-triazine-3-carboxylic acid (XXXVII) is obtained in theoretical yields. On heating (XXXVII) decarboxylates to the triazino-amine (XXXVIII), which in turn can be hydrolysed by hot diluted alkalis to 5-hydroxy-6-phenyl-*as*-triazine (XXXIX).

5-Hydroxy-6-phenyl-*as*-triazine (XXXIX) has also been prepared by an independent synthesis and so additional evidence of the structures of all triazine derivatives described in this work was obtained. 3-Mercapto-5-hydroxy-6-phenyl-*as*-triazine (XLV), prepared by the method of Bougault,[6] yields the corresponding 3-hydrazino-*as*-triazine (XLVI) when treated with hydrazine in boiling butanol. Oxidation of the

[6] J. Bougault and L. Daniel, *C.R. Acad. Sci., Paris* **186**, 151 (1928).

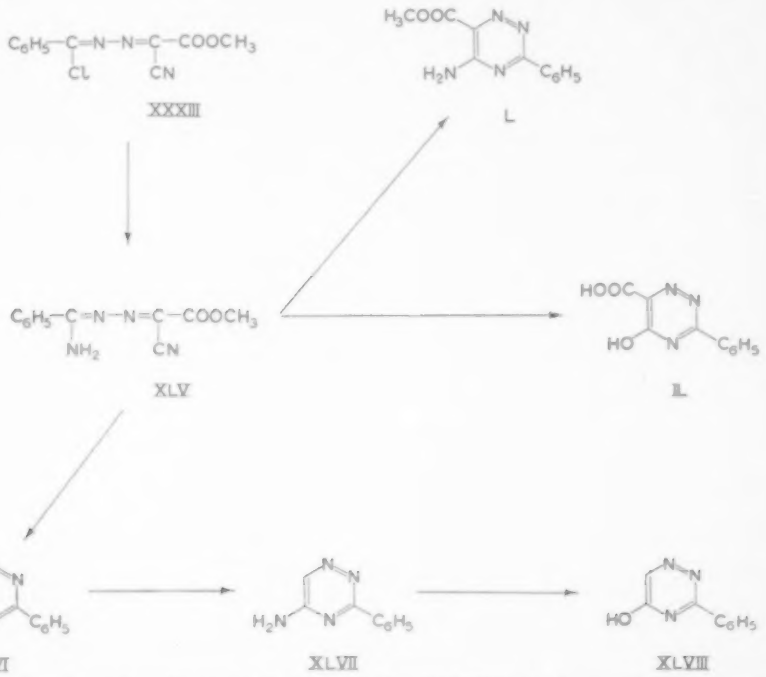

XXX
XXIX
XXXI
XXXIV
XXXII
XXXIII
XXXVI
XXXV
XL
XXXVII
XLI
XXXIX
XXXVIII
XLII
XLIV
XLIII
LI

hydrazine group by yellow mercuric oxide gives 5-hydroxy-6-phenyl-*as*-triazine (XXXIX) identical with the product obtained by decarboxylating acid (XL).



XLV XLVI XXXIX

Formation of the *as*-triazine nucleus from the amino ester (XXXV) is also possible without affecting the carbomethoxyl group by operating in anhydrous ethanol in presence of a sodium alkoxide. 3-Carbomethoxy-5-amino-6-phenyl-*as*-triazine (XLI) can be converted into the corresponding hydrazide (XLII) and Curtius degradation of the latter affords 3-amino-5-hydroxy-6-phenyl-*as*-triazine (XLIV). Alkaline hydrolysis of the carbamate (XLIII) also affects the 5-amino group to give the 5-hydroxy derivative.



XXXIII L

XLV IL

XLVI XLVII XLVIII

From benzene mother-liquors of chloronitrile (XXXII) the lower-melting more-soluble isomer 1-phenyl-1-chloro-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXIII) can be isolated. Experiments carried out in order to purify it having failed, the crude isomer (XXXIII) was treated with ammonia in dioxan solution so that the resulting aminonitrile (XLV) could then be more easily purified by crystallisation from ethanol.

(XLV) when treated with potassium carbonate yields 3-phenyl-5-amino-6-carboxy-*as*-triazine (XLVI) and, by decarboxylation of the latter, 3-phenyl-5-amino-*as*-triazine (XLVI) is obtained. Hydrolysis of the aminotriazine (XLVII) affords 3-phenyl-5-hydroxy-*as*-triazine (XLVIII) while 3-phenyl-5-hydroxy-*as*-triazine-6-carboxylic acid (IL) is obtained by treatment of the amino ester (XLV) with caustic alkalis.

3-Phenyl-5-hydroxy-*as*-triazine-6-carboxylic acid (IL) behaves like a strongly acidic substance and it can be displaced from its salts only by strong mineral acids and furnishes sparingly soluble salts with calcium and barium. Sodium ethoxide affords closure of the *as*-triazine nucleus from the amino ester (XLV) without affecting the carbomethoxyl group and yields 3-phenyl-5-amino-*as*-triazine-6-carboxylic acid methyl ester (L).

EXPERIMENTAL*

1:4-*Diphenyl*-1-*chloro*-4-*cyano*-2:3-*diazabuta*-1:3-*diene* (IX). To a stirred solution of 3:5-diphenyl-4-nitrosopyrazole (III, R = R′ = C_6H_5) (10 g) in 300 ml of boiling anhydrous chloroform, phosphorus pentachloride (13 g) in 100 ml of chloroform was added in small portions. After being set aside for a few hours at room temperature, the solution was repeatedly washed with cold water, dried over calcium chloride and evaporated. The golden-yellow residue crystallised as needles from ethanol (yield 8·2 g), m.p. 138° (Found: C, 67·61; N, H, 3·81; N, 15·33. $C_{15}H_{10}N_3Cl$ requires C, 67·41; H, 3·74; N, 15·73 per cent).

1:4-*Diphenyl*-1-*amino*-4-*cyano*-2:3-*diazabuta*-1:3-*diene* (X). 1:4-Diphenyl-1-chloro-4-*cyano*-2:3-diazabuta-1:3-diene (IX) (15 g) was dissolved in 150 ml of dioxan and treated with dry ammonia gas. Ammonium chloride separated, and after 30 min the flow of ammonia was discontinued, water was added (100 ml) and the yellow precipitate was collected, and recrystallised from ethanol, m.p. 170° (yield 12·5 g) (Found: N = 22·35. $C_{15}H_{12}N_4$ requires N = 22·58 per cent).

3:6-*Diphenyl*-5-*amino*-as-*triazine* (XI). 1:4-Diphenyl-1-amino-4-cyano,-2:3-diazabuta-1:3-diene (X) (12·5 g) was dissolved in 150 ml ethanol and 6 ml of 30% sodium hydroxide were added. After being heated under reflux for 15 min, the solution was completely decolorised and on cooling 10·5 g of the triazine separated as needles, which were recrystallised from ethanol, m.p. 219° (Found: N, 22·57. $C_{15}H_{12}N_4$ requires N, 22·58 per cent).

The aminotriazine gives stable salts with several strong mineral acids. When treated with potassium permanganate in dilute sulphuric acid solution, the violet-red permanganate was precipitated (Found: Mn, 14·81. $C_{15}H_{13}O_8N_4Mn$ requires Mn, 14·94 per cent).

3:6-*Diphenyl*-5-*hydroxy*-as-*triazine* (XII). 3:6-Diphenyl-5-amino-*as*-triazine (XI) (10·5 g) was dissolved in 90 ml of 48% hydrobromic acid and heated under reflux for 3 hr. After cooling, the precipitate was collected on a sintered-glass funnel and recrystallised from acetic acid, m.p. 274–276° (yield 9·5 g); colourless crystals, soluble in alkalis, insoluble in water and sparingly in the usual organic solvents were obtained (Found: N, 16·75. $C_{15}H_{11}ON_3$ requires N, 16·86 per cent).

3:6-*Diphenyl*-5-*chloro*-as-*triazine* (VIII). A mixture of 3-6-diphenyl-5-hydroxy-*as*-triazine (XII) (4 g) and phosphorus pentachloride (5·6 g) in 8 ml of dry toluene was heated under reflux for 3 hr. The toluene solution was thoroughly washed with water, dried over calcium chloride and then evaporated. The residual material (3·3 g) was crystallised from benzene, m.p. 132–134° (Found: N, 15·59. $C_{15}H_{10}N_3Cl$ requires N, 15·73 per cent).

3:6-*Diphenyl*-5-*hydrazino*-as-*triazine* (XIV). 3:6-Diphenyl-5-chloro-*as*-triazine (VIII) (0·64 g) was dissolved in anhydrous ice-cold dioxan (50 ml) and treated with

* Melting points are not corrected.

8 ml of a 5% solution of hydrazine hydrate in dioxan. The mixture was left at room temperature for 2 days, and evaporated to dryness under reduced pressure. The residual solid was collected and crystallised from ethanol. Orange needles soluble into dilute acids, sintering at 217–218°, and melting over 300° were obtained (Found: N, 26·86. $C_{15}H_{13}N_5$ requires 26·61 per cent).

3:6-*Diphenyl*-as-*triazine* (XV). 3:6-Diphenyl-5-hydrazino-*as*-triazine (XIV) (0·15 g) was dissolved in 6 ml of ethanol containing 0·29 g of yellow mercuric oxide and heated under reflux for 1 hr. The cooled suspension was filtered and diluted with water, and the crude precipitate was collected, dried under vacuum and slowly sublimed at 150° and a pressure of 16 mm, m.p. 156–157° (Found: N, 17·93. $C_{15}H_{11}N_3$ requires N, 18·03 per cent).

3:6-*Diphenyl*-5-*thiol*-as-*triazine* (XIII). Sodium (10 mg) was dissolved in 20 ml anhydrous ethanol and the resulting sodium ethoxide solution was first saturated in the cold with hydrogen sulphide and then treated with 3:6-diphenyl-5-chloro-*as*-triazine (VIII) (0·1 g). After the solution had been heated under reflux for 1 hr, 1 ml of acetic acid was added and the mixture was concentrated on a steam-bath. The orange coloured precipitate was collected and crystallised as a monohydrate from dilute ethanol (Found: N, 14·63. $C_{15}H_{11}N_3S{\cdot}H_2O$ requires N, 14·84 per cent).

Reaction between phosphorus pentachloride and 4-*nitroso*-3:5-*dimethylpyrazole* (XVI) 5-*Hydroxy*-3:6-*dimethyl*-as-*triazine* (XX). A solution of 4-nitroso-3:5-dimethylpyrazole (XVI) (11 g)[7] in anhydrous chloroform (70 ml) was slowly added to a stirred water-cooled supension of phosphorus pentachloride (28 g) in 150 ml of anhydrous chloroform while the temperature was kept-below 25°. When the addition had been completed, the chloroform solution was rapidly washed with ice-cold water, dried over calcium chloride and evaporated. The residue was dissolved in light petroleum, treated with Norit, filtered, evaporated under reduced pressure and then distilled under 0·5 mm of mercury. At 55–60°, a pale-yellow liquid (3 g) with a pungent odour was collected. It contained chlorine and had to be kept out of contact with air. In a moist atmosphere after 48 hr it slowly decomposed with evolution of hydrogen chloride to yield (XX), which was purified by crystallisation from water to give colourless plates, m.p. 139–140° (Found: C, 47·87; H, 5·84; N, 33·49. $C_3H_7ON_3$ requires C, 48·00; H = 5·60. N, 33·60 per cent).

The chlorinated substance (1 g) was dissolved in 15 ml of ethanol and treated with 1·1 ml of morpholine. A yellow basic solid was immediately precipitated, and it was recrystallised from water m.p. 115° (Found: N, 28·72. $C_9H_{14}ON_4$ requires N, 28·86 per cent).

Reaction between phosphorus pentachloride and 3-*methyl*-4-*nitroso*-5-*phenylpyrazole* (XXII): 1-*phenyl*-1-*chloro*-4-*methyl*-4-*cyano*-2:3-*diazabuta*-1:3-*diene* (XXIII). 3-Methyl-4-nitroso-5-phenylpyrazole (XXII) (18·7 g) in 200 ml of anhydrous chloroform was slowly added to a cold stirred suspension of 41·6 g phosphorus pentachloride in 300 ml of anhydrous chloroform. When the addition had been completed, the solution was left at room temperature for 2 hr and then washed with cold water and dried over calcium chloride. After evaporation of the chloroform, the residue was dissolved in light petroleum, and the solution was treated with Norit and filtered, the solvent was evaporated under reduced pressure and the residue was distilled *in vacuo*. The product boiling at 115–117°/5 mm was collected and recrystallised from light

[7] L. Wolff, *Liebigs Ann.* **325**, 193 (1902).

petroleum, m.p. 51°. The substance contained chlorine and had to be stored out of contact with air (Found: C, 58·43; H, 4·06, N, 20·12. $C_{10}H_8N_2Cl$ requires C, 58·53; H, 3·90; N, 20·48 per cent).

1-*Phenyl*-1-N-*morpholino*-4-*cyano*-4-*methyl*-2:3-*diazabuta*-1:3-*diene* (XXIV). When 1-phenyl-1-chloro-4-methyl-4-*cyano*-2:3-diazabuta-1:3-diene (XXIII) (1 g) was treated with morpholine (0·85 g), a pale-yellow solid was immediately formed, which after recrystallisation from ethanol had m.p. 115° (Found: N, 21·42. $C_{14}H_{16}ON_4$ requires N, 21·83 per cent). When 0·5 g of this product was heated under reflux for a short time in dilute hydrochloric acid (10 ml), colourless needles were obtained on cooling and were crystallised from water, m.p. 74°. The substance was identical with N-benzoylmorpholine (XXV)[8] with which it showed no depression on a mixed melting point determination.

1-*Phenyl*-1-N-*anilino*-4-*cyano*-4-*methyl*-2:3-*diazabuta*-1:3-*diene* (XXVII). To a solution of 1-phenyl-1-chloro-4-methyl-4-cyano-2:3-diazabuta-1:3-diene (XXIII) in anhydrous ether (15 ml) freshly distilled aniline (0·91 g) was added. In a short time the yellow solid that was precipitated was collected, washed thoroughly with water and crystallised from methanol to give yellow needles of a basic character, m.p. 138° (Found C, 72·99; H, 5·24. $C_{16}H_{14}N_4$ requires C, 73·28; H, 5·34 per cent).

1-*Phenyl*-1-*amino*-4-*cyano*-4-*methyl*-2:3-*diazabuta*-1:3-*diene* (XXVI). Dry ammonia was bubbled into a solution of 1-phenyl-1-chloro-4-methyl-4-cyano-2:3-diazabuta-1:3-diene (XXIII) (1 g) in anhydrous ether (15 ml) until ammonium chloride had completely separated. After the ammonium salt had been removed by filtration, evaporation of the solvent yielded a crystalline solid, m.p. 222°, after recrystallisation from water or dilute ethanol (Found: C, 64·77; H, 5·32. $C_{10}H_{10}N_4$ requires C, 64·51; H, 5·37 per cent).

3-*Phenyl*-5-*hydroxy*-6-*methyl*-as-*triazine* (XXVIII). When left in contact with air at room temperature, 1-phenyl-1-chloro-4-methyl-4-cyano-2:3-diazabuta-1:3-diene (XXIII) reacted slowly, absorbing moisture and evolving hydrogen chloride. The resulting product was crystallised twice from water. It can also be sublimed or distilled under reduced pressure (Found: C, 64·19; H, 4·99; N, 22·19. $C_{10}H_9ON_3$ requires C, 64·17; H, 4·81; N, 22·45 per cent).

3-*Phenyl*-4-*nitroso*-5-*carbomethoxypyrazole* (XXIX). Methylacetophenone oxalate (I; $R = C_6H_5$, $R' = COOCH_3$) (20 g)[9] was dissolved into 100 ml of ice-cold glacial acetic acid and treated with a concentrated aqueous solution of sodium nitrite (7 g). To the stirred solution 12·5 ml of 85% hydrazine hydrate dissolved in 20 ml of acetic acid was slowly added. The temperature was kept between 10° and 15°. Addition of hydrazine must immediately follow that of sodium nitrite to obtain satisfactory yields in this preparation.* After addition of hydrazine the deep-green solution was kept in an ice-bath for 30 min and then diluted with 1 l. of ice-cold water. A crystalline colourless solid was precipitated and after 2 hr it was collected, washed with water and crystallised from 50% ethanol, to yield monohydrated prisms (yield 18 g) m.p. 104° (dec.) (Found: N, 16·62. $C_{11}H_9N_3O_3 \cdot H_2O$ requires N, 16·86 per cent).

3-*Phenyl*-4-*nitro*-5-*carbomethoxypyrazole* (XXXI). 3-Phenyl-4-nitroso-5-carbomethoxypyrazole (XXIX) (0·7 g) was dissolved in 80% nitric acid (8 ml) and heated on

* The intermediate methyl*iso*nitroso acetophenone oxalate (II; $R = C_6H_5$, $R' = COOCH_3$) was rapidly hydrolysed to give hydrogen cyanide, oxalic acid and benzoic acid.

[8] L. Knorr, *Leibigs Ann.* **301**, 1 (1898).
[9] W. Wislicenus and W. Stoeber, *Ber. Dtsch. Chem. Ges.* **35**, 539 (1902).

a steam-bath until evolution of oxides of nitrogen subsided. The cool solution was diluted with 25 ml of water and extracted with ether, and the extracts in turn were treated with 5 ml of diluted sodium hydroxyde. On acidification 0·48 g of the pale yellow nitro compound were collected (yield 70 per cent), m.p. 193° after recrystallisation from water (Found: N, 17·22. $C_{11}H_9N_3O_4$ requires N, 17·00 per cent).

3-Phenyl-4-amino-5-carbomethoxypyrazole (XXX). 3-Phenyl-4-nitroso-5-carbomethoxypyrazole (XXIX) (0·5 g) was dissolved in 50% acetic acid (12 ml) and to the boiling solution iron dust (0·34 g) was added portionwise. Undissolved material was removed by filtration of the hot solution from which, on cooling, a solid colourless material separated (yield 0·28 g), m.p. 168–169°, after recrystallisation from water or benzene (Found: N, 19·08. $C_{11}H_{11}N_3O_2$ requires N, 19·35 per cent).

Reaction between phosphorus pentachloride and 3-phenyl-4-nitroso-5-carbomethoxypyrazole (XXIX): *1-cyano-1-phenyl-4-chloro-4-carbomethoxy-2:3-diazabuta-1:3-diene* (XXXII) *and 1-chloro-1-phenyl-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene* (XXXIII). To a stirred boiling suspension of phosphorus pentachloride (66 g) in dry chloroform (200 ml), a solution of 3-phenyl-4-nitroso-5-carbomethoxypyrazole (XXIX) (36 g) in chloroform (700 ml) was slowly added. Then 15 min after the addition had been completed heating was discontinued, the solution was cooled to 20° and 100 ml of water were added while temperature was kept below 25°. Stirring was continued for 10 min at room temperature, the water layer was decanted, and the chloroform layer was washed repeatedly with water, dried over calcium chloride and evaporated at reduced pressure. A yellow solid material that remained which was crystallised from ethanol (yield 27·5 g, 70 per cent). The mixture of isomers (XXXII) and (XXXIII) obtained melted between 98 and 110° (Found: C, 53·06; H, 3·30; N, 16·81. $C_{11}H_8O_2N_3Cl$ requires C, 53·01; H, 3·21; N, 16·86 per cent).

Separation of the two isomers was accomplished by fractional crystallisation from benzene. 1-Phenyl-1-cyano-4-chloro-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXII) was obtained in a pure state after three crystallisations as yellow needles melting at 110° (yield 10 g). When 1 g of this material was dissolved in ethanol (15 ml) and a concentrated ethanolic solution of thiourea (0·335 g) was added, after a brief heating on a steam-bath, thiazolinone (XXXIV) was obtained in theoretical yield as yellow needles, m.p. 221° (Found: N, 26·70. $C_{11}H_7ON_5S$ requires N, 27·23 per cent). From the benzene mother-liquors 16 g of a substance were obtained melting at 87–88°, which consisted chiefly of 1-phenyl-1-chloro-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXIII) and contained some of the higher-melting isomer (XXXII) (slightly positive thiourea test).

1-Cyano-1-phenyl-4-amino-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXV). 1-Phenyl-1-cyano-4-chloro-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXII) (8·2 g) was dissolved in dioxane (60 ml) and a saturated methanolic ammonia solution (9·5 ml) was added with cooling in ice. When the reaction was complete, a sample, after being washed with water, gave a negative Beilstein test for halogens. Then 500 ml of water was added, the precipitate was collected and crystallised from ethanol as pale-yellow flakes, very soluble in dioxan, ethanol and benzene, and sparingly in water (yield 6·75 g, 91 per cent), m.p. 132–133° (Found: N, 24·46; $C_{11}H_{10}N_4O_2$ requires N, 24·34 per cent). When the dioxan solution of the chloro ester (XXXII) was treated with dry ammonia gas for 15–20 min 1-phenyl-1-cyano-4-amino-4-carbamino-2:3-diazabuta-1:3-diene (XXXVI) was formed as pale-yellow needles, soluble in dioxan

and ethanol, and sparingly in water, m.p. 193°, after recrystallisation from ethanol (Found: N, 32·22. $C_{10}H_{10}N_5O$ requires N, 32·40 per cent).

3-Carboxy-5-amino-6-phenyl-as-*triazine* (XXXVII). 1-Phenyl-1-cyano-4-amino-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXV) (13 g) was suspended in water (250 ml), potassium carbonate (8 g) was added and the mixture was heated under reflux for 20 min. On cooling and acidification with acetic acid 12·4 g (96 per cent) of triazine was collected as colourless crystals after recrystallisation from water, m.p. 178° (dec.) (Found: N, 25·98. $C_{10}H_8N_4O_2$ requires N, 25·92 per cent).

5-Amino-6-phenyl-as-*triazine* (XXXVIII). 3-Carboxy-5-amino-6-phenyl-*as*-triazine (XXXVII)(5 g) was heated at 180° for 45 min in an oil-bath. After cooling the material was dissolved in hot water, treated with Norit and filtered. The product being monohydrated, the anhydrous 5-amino-6-phenyl-*as*-triazine was obtained by sublimation at 170° in a 2 Torr. vacuum (yield 2·1 g) m.p. 127° (Found N, 32·59. $C_9H_8N_4$ requires N, 32·55 per cent).

3-Carboxy-5-hydroxy-6-phenyl-as-*triazine* (XL). 1-Phenyl-1-cyano-4-amino-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXV) (1 g) was dissolved in boiling water (15 ml) and 30% sodium hydroxyde solution was added (0·8 ml). The solution was heated under reflux for 10 min, and then cooled and acidified with acetic acid to give monohydrated colourless crystals (yield 0·76 g) m.p. 265°, after recrystallisation from water (Found: N, 17·90. $C_{10}H_7N_3O_3 \cdot H_2O$ requires N, 17·87 per cent).

3-Hydrazino-5-hydroxy-6-phenyl-as-*triazine* (XLVI). 3-Mercapto-5-hydroxy-6-phenyl-*as*-triazine (XLV) (5 g) was dissolved in *n*-butanol (150 ml) and 85% hydrazine hydrate solution (10 ml) was slowly added. The hydrazine salt immediately separated and, when the solution was heated under reflux, it was slowly converted into the hydrazino derivative with evolution of hydrogen sulphide. After 3 hr the reaction was completed and the solid product that separated from the cold solution was collected and dissolved into hot water. Hydrochloric acid was added and the hydrochloride was obtained on cooling as colourless crystals (yield 2·5 g, m.p. 292–293° (Found: N, 29·37. $C_9H_9N_5O \cdot HCl$ requires N, 29·28 per cent).

5-Hydroxy-6-phenyl-as-*triazine* (XXXIX). (*i*) 5-Amino-6-phenyl-*as*-triazine (XXXVIII) (1 g) was dissolved in water (10 ml), 1 ml of 30% sodium hydroxide added and the solution was heated under reflux until evolution of ammonia ceased. On cooling and acidification with hydrochloric acid, colourless crystals were obtained (0·78 g), m.p. 208°, after recrystallisation (from water or ethanol) (Found: N, 24·25. $C_9H_7N_3O$ requires N, 24·27 per cent).

(*ii*) 3-Carboxy-5-hydroxy-6-phenyl-*as*-triazine (XL) (0·5 g) was heated in an oil-bath at 260–270° until evolution of carbon dioxide ceased. The residual material was dissolved into hot water, treated with Norit and filtered. Colourless crystals were obtained melting at 208° identical with the above described product.

(*iii*) 3-Hydrazino-5-hydroxy-6-phenyl-*as*-triazine (XLVI) hydrochloride (2g) was dissolved in a mixture of ethanol (80 ml) and water (10 ml). A concentrated aqueous solution of sodium hydroxide (0·52 g) was added and then in small portions 3·5 g of finely ground yellow mercuric oxide. The mixture was heated under reflux until the yellow colour disappeared, then filtered, acidified with hydrochloric acid, diluted with water (50 ml), treated with hydrogen sulphide, filtered and concentrated on a steam-bath. The collected solid material was crystallised from water (yield 0·63), m.p.

208°. The substance was identical with the hydroxy-*as*-triazine described above with which it showed no depression on a mixed melting point.

3-*Carbomethoxy*-5-*amino*-6-*phenyl*-as-*triazine* (XLI). To 1-Phenyl-1-cyano-4-amino-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXV) (5 g) in hot anhydrous methanol (100 ml) was added absolute methanol (10 ml) to which 0·2 g of sodium had previously been added. After being heated under reflux for 1 hr, the hot solution was filtered and, after cooling, colourless crystals were collected and recrystallised from ethanol (1 g), m.p. 229° (Found: N, 24·39. $C_{11}H_{10}N_4O_2$ requires N, 24·34 per cent).

3-*Carbohydrazino*-5-*amino*-6-*phenyl*-as-*triazine* (XLII). 3-Carbomethoxy-5-amino-6-phenyl-*as*-triazine (XLI) (0·13 g) was dissolved in hot ethanol (10 ml) and 0·5 ml of 85% hydrazine hydrate solution were added. The product was purified by being dissolved in dilute hydrochloric acid and reprecipitated with ammonia solution, and then washed with hot ethanol, m.p. 261–262° (Found: N, 36·51. $C_{10}H_{10}N_6O$ requires N, 36·52 per cent).

3-*Amino*-5-*hydroxy*-6-*phenyl*-as-*triazine* (XLIV). To a solution of 0·13 g of 3-carbohydrazino-5-amino-6-phenyl-*as*-triazine (XLII) (0·13 g) in cold dilute hydrochloric acid (15 ml), sodium nitrite (0·047 g) dissolved in a little water was added. The azide (LI) immediately separated as a green-yellow solid, which was filtered off and dried in a desiccator over phosphorus pentoxide under vacuum. The dry azide was heated under reflux in ethanol until evolution of nitrogen ceased, and the solvent was then distilled under reduced pressure and the residue was taken up with water (10 ml) to which 32% sodium hydroxide solution (0·5 ml) had been added. The mixture was heated under reflux for 1 hr, and after cooling it was neutralised with acetic acid, when the crude product that separated was collected and crystallised from water, m.p. 329° (Found: N, 29·47. $C_9H_8N_4O$ requires N, 29·78 per cent).

1-*Phenyl*-1-*amino*-4-*cyano*-4-*carbomethoxy*-2:3-*diazabuta*-1:3-*diene* (XLV). Crude 1-phenyl-1-chloro-4-cyano-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XXXII) (6 g) was dissolved in dioxan (50 ml) and a saturated solution of ammonia in methanol (6 ml) was added, the solution being cooled in ice; water (300 ml) was then added and the precipitate was collected and recrystallised from methanol as yellow needles, m.p. 159° (Found N, 24·27. $C_{11}H_{10}N_4O_2$ requires N, 24·34 per cent).

3-*Phenyl*-5-*amino*-6-*carboxy*-as-*triazine* (XLVI). 1-Phenyl-1-amino-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XLV) (3 g) was added to an aqueous potassium carbonate solution (1·8 g and 100 ml of water) and heated under reflux for about 15 min. When the yellow colour of the aminonitrile had completely disappeared, the solution was acidified with acetic acid and, on cooling, the crystalline precipitate was collected, and recrystallised from acetic acid, m.p. 184° (Found: N, 25·76. $C_{10}H_8N_4O_2$ requires N, 25·92 per cent).

3-*Phenyl*-5-*amino*-as-*triazine* (XLVII). 3-Phenyl-5-amino-6-carboxy-*as*-triazine (XLVI) (0·25 g) was heated at 190–200° for 1 hr in an oil-bath. After cooling, the material was dissolved in dilute acetic acid and the solution was treated with Norit, filtered and precipitated with ammonia solution to give colourless needles (yield 0·15 g), m.p. 249–250° after recrystallisation from water (Found: N, 32·36. $C_8H_8N_4$ requires N, 32·55 per cent).

3-*Phenyl*-5-*hydroxy*-as-*triazine* (XLVIII). 3-Phenyl-5-amino-*as*-triazine (XLVII) (0·2 g) was suspended in water (10 ml) containing 1 g of sodium hydroxide. The mixture

was heated under reflux until evolution of ammonia ceased, and it was then cooled, filtered and acidified with hydrochloric acid. The crude product was crystallised from water and from ethanol (yield 0·15 g), m.p. 245° (Found: N, 24·10. $C_9H_7N_3O$ requires N, 24·27 per cent).

3-*Phenyl*-5-*amino*-6-*carbomethoxy*-as-*triazine* (L). 1-Phenyl-1-amino-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XLV) (4 g) was dissolved in absolute methanol (60 ml) and a methanolic solution of sodium methoxide (0·2 g of sodium in 20 ml of methanol) was added. The mixture was heated under reflux for 10 min and the product was collected on cooling as straw-coloured crystals (yield 2·3 g), m.p. 232° (Found: N, 24·49. $C_{11}H_{10}N_4O_2$ requires N, 24·34 per cent).

3-*Phenyl*-5-*hydroxy*-6-*carboxy*-as-*triazine* (IL). 1-Phenyl-1-amino-4-cyano-4-carbomethoxy-2:3-diazabuta-1:3-diene (XLV) (1 g) was dissolved in hot water (15 ml) containing 0·3 g of sodium hydroxide. The solution was heated under reflux until evolution of ammonia ceased and it was then cooled, filtered and acidified with hydrochloric acid to give a product, m.p. 179–180° (Found: N, 19·60. $C_{10}H_7N_3O_3$ requires N, 19·35 per cent).

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A STUDY OF LEUCOANTHOCYANIDINS OF PLANTS—I

ISOMERS OF LEUCODELPHINIDIN FROM KARADA BARK AND EUCALYPTUS GUM

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Abstract—The leucoanthocyanidin of Karada bark (*Cleistanthus collinus*) has been isolated, and its acetate and methyl ether have been prepared and their properties and reactions studied. It is found to be a (−)-leucodelphinidin (5:7:3′:4′:5′-pentahydroxyflavan-3:4-diol). A *dextro*-rotatory leucodelphinidin is found in the kino (gum) obtained from *Eucalyptus pilularis* and it gives a different series of derivatives.

ALTHOUGH it is more than 30 years since the first study[1] of leucoanthocyanidins appeared and considerable interest has been shown in regard to their occurrence and function, the more common of the naturally occurring leucoanthocyanidins have not yet been isolated in a pure condition. This has been considered to be due to difficulties arising from their high instability and their discouraging properties. The only successful cases so far recorded are melacacidin[2] (which belongs to a special type and whose definite solubility in boiling ether helped the separation from the accompanying substances) and mollisacacidin[3] (leucofisetinidin). Consequently, efforts to elucidate precisely the part played by them in tanning, in dyeing, in regard to the taste and function of foodstuffs, in drugs and as antioxidants could not be made. A programme of exploration was therefore undertaken for suitable sources and suitable methods by which leucoanthocyanidins could be obtained pure in adequate quantity for experiments on their function. A good source has now been found in Karada bark, from which a pure sample of leucodelphinidin has been obtained.

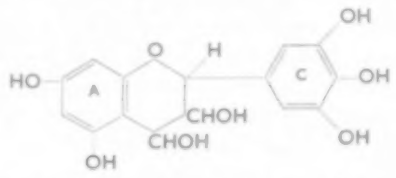
Karada bark is a popular tanning material. It is obtained from *Cleistanthus collinus*, a small tree found all over India, and it has been estimated that 10,000–12,000 tons of the bark can be collected every year. It has been reputed to contain a very high percentage of tannin and to yield good leather. Exploratory experiments indicated that it contains a single leucoanthocyanidin in good concentration. In actual isolation the crude sample amounted to 8–10 per cent of the air-dry bark, although after drastic purification only a 3 per cent yield of leucoanthocyanidin was obtained. For securing good yields it is necessary to use the bark as fresh as possible and the extraction has to be carried out at low temperatures, preferably with non-hydroxylic solvents, in order to avoid decomposition and oxidation. In our experiments extraction with low-boiling light petroleum (boiling range 40–60°) removed fatty matter, and subsequent extraction with acetone successfully removed all the leucoanthocyanidin. For purification the crude sample is taken up in ethyl acetate

[1] O. Rosenheim, *Biochem. J.* **14**, 178 (1920).
[2] F. E. King and W. Bottomley, *Chem. & Ind.* 1368 (1953); *J. Chem. Soc.* 1399 (1954).
[3] H. H. Keppler, *J. Chem. Soc.* 2721 (1957).

and subjected to fractional precipitation with light petroleum, whereby impurities are removed first and the leucoanthocyanidin is eventually obtained as a crystalline powder. Repetition of this process yields an almost colourless sample.

It has the molecular formula $C_{15}H_{14}O_8$, is *laevo*rotatory and gives the reactions typical of leucoanthocyanidins. A convenient crystalline derivative is the pentamethyl ether, obtained by means of diazomethane, and this subsequently forms a diacetate. By boiling with alcoholic hydrochloric acid the corresponding anthocyanidin and its pentamethyl ether have been obtained. The former has been identified by its colour reactions, chromatography and absorption spectra as delphinidin. Delphinidin chloride has also been obtained in a crystalline form from the leucoanthocyanidin by adopting a modification of the method used by Robinson[4] for butea gum.

Degradations were carried out with the methyl ether. Oxidation with neutral permanganate yielded trimethylgallic acid. The results of analysis and also the behaviour of the leucoanthocyanidin and the methyl ether with periodic acid conclusively showed that the compound is a flavandiol. The diol structure was further confirmed by the study of the infra-red spectrum of the methyl ether, which contained no carbonyl frequency. Hence the leucodelphinidin of Karada bark should be represented as 5:7:3′:4′:5′-pentahydroxy flavan 3:4-diol (I).



Eucalyptus gum (kino) has been used as a drug for a long time. A number of species of *Eucalyptus* are grown in India and *Eucalyptus pilularis* is one that is common in the Nilgiris. Leucodelphinidin has been extracted from this gum by adopting the same process as described above. It agreed with the leucodelphinidin obtained from Karada bark in its chemical properties. However, it is found to be *dextro*rotatory and the melting points of the derivatives are also different. It is therefore clear that the leucoanthocyanidin occurs in more than one form in nature. A detailed study of the stereochemistry involved is in progress.

EXPERIMENTAL

Isolation of the leucoanthocyanidin from Karada bark

The fresh bark of *Cleistanthus collinus* was obtained from the Central Leather Research Institute, Madras. The powdered bark (1 kg) was extracted repeatedly with low-boiling light petroleum. Concentration of the extracts yielded a colourless substance, which on crystallisation from ethanol had m.p. 141–142°. It did not give any characteristic colour with ethanolic ferric chloride, magnesium and hydrochloric acid, and zinc and hydrochloric acid, but it developed a red colour with acetic anhydride and concentrated sulphuric acid. The residual bark was first extracted with ether and subsequently with cold acetone. The ether extract did not yield any crystalline substance. The first acetone extract was deep red in colour, and the intensity of

[4] G. M. Robinson (Mrs.), *J. Chem. Soc.* 1157 (1937).

the colour diminished with further extractions. The combined acetone extract was evaporated under reduced pressure to remove the acetone completely. The red sticky residue was extracted repeatedly with cold ethyl acetate. The ethyl acetate extract was dried over freshly ignited magnesium sulphate and then concentrated under reduced pressure. By gradual addition of light petroleum (boiling range 40–60°) coloured impurities were precipitated first. Further addition of light petroleum and cooling in a refrigerator yielded the leucoanthocyanidin as a crystalline mass. The process was repeated several times in order to obtain an almost colourless sample (30 g). It darkens and shrinks at 220° and does not melt up to 350° (Found: C, 52·1, 51·8; H, 5·3, 5·0. $C_{15}H_{14}O_8,1{\cdot}5H_2O$ requires C, 51·6; H, 4·9 per cent). The product was insoluble in light petroleum, ether, chloroform and benzene, but freely soluble in water, ethanol and acetone. With 10% ethanolic hydrochloric acid it developed immediate purple colour even in the cold; this deepened on keeping or on heating. With aqueous hydrochloric acid no colour was developed in the cold, but on heating a purple colour was produced along with the separation of a reddish brown amorphous material. With ethanolic ferric chloride the substance gave a blue colour. The ultra-violet spectrum of the leucoanthocyanidin showed a distinct maximum at 282 mμ and minimum at 250 mμ.

Conversion of the leucoanthocyanidin into delphinidin chloride

The leucoanthocyanidin (1 g) was suspended in water (15 ml) containing sodium acetate (2 g) and boiled for 8 min. The boiling was continued for another minute more, after the addition of fused zinc chloride (2 g). The reaction mixture was cooled thoroughly and then treated with a saturated aqueous solution of picric acid (18 ml) and the mixture was heated under reflux for 10 min. Ethanolic hydrochloric acid (200 ml, 8 per cent) was added to the reaction mixture and the heating under reflux was continued for 2 hr. The mixture was diluted with water, kept in the refrigerator for 2–3 hr, and filtered to remove the phlobaphene that separated out, and then the filtrate was extracted with *iso*amyl alcohol. The colouring matter was transferred to 1 per cent hydrochloric acid solution by the addition of light petroleum. The acid solution was washed thoroughly with benzene and concentrated at ordinary temperature over potassium hydroxide in a vacuum desiccator. The delphinidin chloride that separated was filtered off (yield 100 mg).

The following observations were made with the 1 per cent hydrochloric acid extract of the anthocyanidin chloride: (*a*) ferric chloride reaction, positive; (*b*) extraction with cyanidin reagent, no extraction; and (*c*) R_F (circular) with phenol–water, lower layer at 30°, 0·54. The ethanolic hydrochloric acid solution of the anthocyanidin chloride had an absorption maximum at 552 mμ.

Acetylation of the leucoanthocyanidin

Treatment of the leucoanthocyanidin (1 g) with acetic anhydride (10 ml) and pyridine (4 ml) in the cold for 48 hr yielded a solid (0·7 g), which crystallised from ethyl acetate and light petroleum as colourless short needles and rectangular prisms, m.p. 260° (dec. with sintering from 250°) (Found: C, 56·0; H, 4·7. $C_{29}H_{28}O_{15}$ requires C, 56·5; H, 4·5 per cent). It gave no colour with ethanolic ferric chloride. When the ethanolic solution of the acetate was boiled with concentrated hydrochloric acid, a pink colour developed.

Methylation of the leucoanthocyanidin

This was carried out with both diazomethane and dimethyl sulphate, the former reagent yielding a purer product.

Method (a). A solution of the leucoanthocyanidin (1 g) in methanol (70 ml) was treated at 0° with an excess of an ethereal solution of diazomethane until the mixture acquired a yellow colour. After the mixture had been kept for 24 hr at 0°, most of the solvent was removed and a small amount of water was added to precipitate the leucoanthocyanidin methyl ether (0·8 g). It crystallised from methanol as colourless tiny prisms, m.p. 160–164°, $[\alpha]_D^{35}$ −53·8° (ca. 0·4 per cent) (Found: C, 61·2; H, 6·2. $C_{20}H_{24}O_8$ requires C, 61·2; H, 6·2 per cent). On being heated with ethanolic hydrochloric acid, it developed a reddish colour. The methyl ether was insoluble in aqueous alkali and gave no colour with ethanolic ferric chloride.

Method (b). A solution of the leucoanthocyanidin (1 g) in dry acetone (100 ml) was heated under reflux with dimethyl sulphate (1·5 ml) and ignited potassium carbonate (5 g) for 6 hr. The potassium salts were removed by filtration, the acetone was evaporated from the filtrate and the residue was treated with cold water. The light coloured solid (0·5 g) did not yield good crystals from methanol and it had m.p. 161° (with sintering at 140°). It did not give any colour with ethanolic ferric chloride, but it developed a reddish colour on being boiled in ethanolic solution with concentrated hydrochloric acid. It was insoluble in aqueous alkali.

Infra-red spectrum. The spectrum of the leucoanthocyanidin methyl ether has been recorded in chloroform solution and the following are the main bands: 6·26 (s), 6·86 (s), 7·20 (m), 7·53 (m), 8·26 (m) and 8·79 μ (s).

Acetylation of the leucoanthocyanidin methyl ether. The methyl ether (0·2 g) was acetylated with acetic anhydride (2 ml) and pyridine (0·5 ml) in the cold for 24 hr. The acetate (0·1 g) crystallised from methanol as small cubes, m.p. 218–220° (Found: C, 60·7; H, 4·8. $C_{24}H_{28}O_{10}$ requires C, 60·5; H, 4·7 per cent).

Potassium permanganate oxidation of the methyl ether. A boiling solution of the leucoanthocyanidin methyl ether (1 g) in acetone (100 ml) was treated during 5 hr with powdered potassium permanganate (5 g) in small lots. After addition of water (10 ml) most of the acetone was removed by distillation and the mixture was decolorised by sulphur dioxide. The solution was extracted with ether and the extract was washed with aqueous saturated sodium bicarbonate. The bicarbonate solution was acidified with hydrochloric acid and then repeatedly extracted with ether. On removal of the ether, a brown sticky residue was obtained; on vacuum sublimation it yielded an acid, m.p. 165–166°, undepressed by an authentic sample of trimethylgallic acid. Circular paper chromatography was carried out, butanol saturated with ammonia being used as the irrigating solvent and bromophenol blue as the developer; a sharp ring was obtained having R_F 0·62. Trimethylgallic acid under similar condition gave R_F 0·60.

Eucalyptus pilularis gum (*kino*)

The sample of the gum was collected from the trees in Sims Park in Coonoor (Nilgiris).

Extraction. The finely powdered gum (600 g) was extracted successively with light petroleum, ether and acetone. The light petroleum extract contained waxy matter and did not yield any crystalline product. A small quantity of a light brown coloured

solid was obtained from the ether extract; its colour reactions indicated it to be triterpenoid. It could not be studied further owing to insufficiency of the material. Acetone extracted the leucoanthocyanidin successfully. It was purified by using a mixture of ethyl acetate and light petroleum as mentioned in the case of Karada bark (yield 12 g) (Found: C, 51·5, 51·4; H, 5·3, 4·9. $C_{15}H_{14}O_8$,1·5H_2O requires C, 51·6; H, 4·9 per cent). It darkens and shrinks at about 230° and does not melt up to 350°. It gave delphinidin chloride with ethanolic hydrochloric acid.

Acetate. The leucoanthocyanidin formed a colourless acetate with acetic anhydride and pyridine. It crystallised from a mixture of ethyl acetate and light petroleum as tiny prisms. It started melting at about 228° and finally decomposed at 240° (Found: C, 57·1; H, 4·0. $C_{29}H_{28}O_{15}$ requires C, 56·5; H, 4·5 per cent).

Methyl ether. The crystalline pentamethyl ether was prepared with diazomethane. It crystallised from methanol as colourless small prisms melting at 180–184° and the mixed m.p. with (—)-leucodelphinidin methyl ether was depressed, $[\alpha]_D^{32}$, + 72·9 (Found: C, 60·1, 60·1; H, 5·5, 6·1. $C_{20}H_{24}O_8$,0·5H_2O requires C, 59·9; H, 6·2 per cent).

Methyl ether diacetate. The methyl ether was acetylated with acetic anhydride and pyridine. The diacetate crystallised from methanol as short rectangular prisms and melted at 225–230°. The mixed m.p. with the methyl ether diacetate obtained from Karada bark was depressed (Found: C, 60·7; H, 4·8. $C_{24}H_{28}O_{10}$ requires C, 60·5; H, 4·7 per cent.).

Oxidation. Oxidation of the methyl ether with potassium permanganate yielded trimethylgallic acid, m.p. 166–167°, undepressed by admixture with an authentic sample.

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SYNTHESIS OF BENZOFURAN DERIVATIVES—II

A NEW SYNTHESIS OF VISNAGIN

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Abstract—Starting with 2-methyl-5:7-dihydroxychromone, an allyl group is introduced into the 6-position by Claisen migration of a 5-allyl ether. The initial protection of the 7-hydroxyl is best effected by tosylation. If the tosyl group is removed before Claisen migration and the C-allyl compound subjected to ozonolysis and ring closure, norvisnagin is obtained in a poor yield and can be methylated to visnagin. In an alternative method the tosyl group is removed just before ozonolysis. For this purpose the previous methylation of the 5-position is advantageous. This route gives visnagin directly in good yield.

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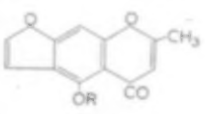
IN part I[1] a new method of synthesis of benzopyronofurans was described. It consisted in building up a furan ring on to a pyrone system. The feasibility of the method was illustrated by the synthesis of a number of angular benzopyronofuran derivatives. Its suitability for the preparation of compounds of the linear type has now been examined, visnagin being taken as the typical example.

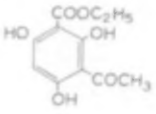
Visnagin is the major component of the seeds of *Ammi Visnaga*, an important plant drug. Its constitution was established by Späth and Gruber[2] as a linear chromonofuran derivative (Ia). The earliest synthesis was by Gruber and Horváth[3], who, starting with the ethyl ester of phloroacetophenonecarboxylic acid (II) built up a furan ring first, then removed the protecting carbethoxy group and finally closed the chromone ring. Later, Davies and Norris[4] and Geissman and Hinreiner[5] carried out the synthesis without the initial introduction of the carbethoxy group. Mixtures were naturally produced and had to be separated at several stages. Both methods involved a large number of steps and the final yield of visnagin was small.



I

(a) R = $-CH_3$

(b) R = $-H$



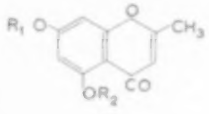
II

The synthesis in which the furan ring is built up last, may be more closely following the process of biosynthesis in plants. This could be expected to lead to a more efficient and a simpler route. In the present case the furan ring closure involves the 6-position and, since nuclear methylation of chromones and flavones[6] is definitely known to

[1] R. Aneja, S. K. Mukerjee and T. R. Seshadri *Tetrahedron* **2**, 203 (1958)
[2] E. Späth and W. Gruber, *Ber. Dtsch. Chem. Ges.* **74**, 1492 (1941).
[3] W. Gruber and K. Horváth, *Mh. Chem.* **81**, 819 (1950).
[4] J. S. H. Davies and W. L. Norris, *J. Chem. Soc.* 3195 (1950).
[5] T. A. Geissman and E. Hinreiner, *J. Amer. Chem. Soc.* **73**, 782 (1951).
[6] S. K. Mukerjee and T. R. Seshadri, *Proc. Ind. Acad. Sci.* A **38**, 207 (1953).

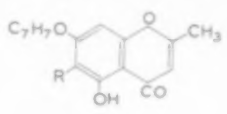
take place in the 6-position, nuclear allylation of 2-methyl-5:7-dihydroxychromone[7] was attempted; it gave only a resinous product. In this connection may be mentioned the similar experience of Bolleter *et al.*,[8] who reported that nuclear allylation of the same chromone with dimethylallyl bromide gives an extremely poor yield.

As an alternative method, Claisen migration was considered. The 7-allyl ether (IIIa) is easily made, but it is known[9] that the allyl group of this ether migrates to the vacant 8-position. On the other hand, the 5-allyl ether (IIIb) could be expected to suffer migration of the allyl group to the 6-position. But for the preparation of this ether (IIIb), the hydroxyl group in the 7-position has to be protected by means of a group capable of easy elimination at a later stage. The benzyl group was first employed; the 7-benzyl ether[7] of 2-methyl-5:7-dihydroxychromone (IIIc) was allylated in the 5-position and subjected to allyl migration. It proceeded satisfactorily to give the 6-allyl compound (IVa). Ozonolysis of this product or its 5-methyl ether, however, did not proceed smoothly. Alternatively, the acetate, 2-methyl-5-acetoxy-6-allyl-7-benzyloxychromone was treated with performic acid followed by hydrolysis with alkali. Though this gave a fair yield of the benzyloxydiol (IVb), which could be debenzylated by catalytic hydrogenation, subsequent fission of the diol (Va) by means of periodic acid did not succeed. Instead of the desired aldehyde (Vb), an iodine-containing product was formed and it was not further investigated.



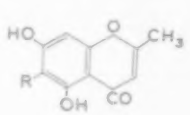
III

(a) $R_1 = -C_3H_5$; $R_2 = -H$
(b) $R_1 = -H$; $R_2 = -C_3H_5$
(c) $R_1 = -C_7H_7$; $R_2 = -H$



IV

(a) $R = -C_3H_5$
(b) $R = -CH_2 \cdot CHOH \cdot CH_2OH$



V

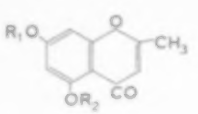
(a) $R = -CH_2 \cdot CHOH \cdot CH_2OH$
(b) $R = -CH_2 \cdot CHO$

The drawback in the foregoing method seemed to be the difficulty of removing the benzyl group in the presence of the allyl substituent. The benzoyl group appeared to be better for this purpose. The partial benzoate (VIa) of the dihydroxychromone was obtained in good yield, but, when it was heated under reflux with allyl bromide and potassium carbonate in acetone medium, besides the normal reaction, there was extensive debenzoylation and allylation of the 7-hydroxyl group thus set free. This route, therefore, became unworkable. Here may be mentioned the observation of Birch *et al.*[10], that deacetylation at the 7-position takes place under similar conditions of methylation.

The above-mentioned difficulties were finally solved by working with the partial tosyl ester (VIb). It could be easily allylated to the 5-allyl ether (VIc), from which the tosyl group could be removed by hydrolysis. Subsequent Claisen migration gave the desired 2-methyl-6-allyl-5:7-dihydroxychromone (VIIa). This was definitely different from the isomeric 8-allylchromone (VIIb).[9] Ozonolysis and final ring

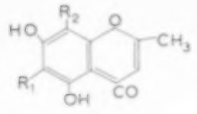
[7] K. C. Gulati, S. R. Seth and K. Venkataraman, *J. Chem. Soc.* 1766 (1934).
[8] A. Bolleter, K. Elier and H. Schmid, *Helv. Chim. Acta* **34**, 186 (1951).
[9] S. S. Chibber, A. K. Ganguly, S. K. Mukerjee and T. R. Seshadri, *Proc. Ind. Acad. Sci.* A **46**, 19 (1957).
[10] A. J. Birch, P. Elliot, S. K. Mukerjee, T. R. Rajagopalan, T. S. R. Seshadri and Varadarajan, *Aust. J. Chem.* **8**, 409 (1955).

closure yielded norvisnagin (Ib).[11] Yields in this series of experiments were good except at the ozonolysis stage.



VI

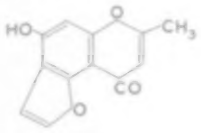
(a) $R_1 = -COC_6H_5$; $R_2 = -H$
(b) R_1 = Tosyl ; $R_2 = -H$
(c) R_1 = Tosyl ; $R_2 = -C_3H_5$



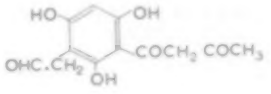
VII

(a) $R_1 = -C_3H_5$; $R_2 = -H$
(b) $R_1 = -H$; $R_2 = -C_3H_5$

Special mention should be made here that the product of the furan ring closure is a single entity, in which cyclisation has proceeded through the 7-hydroxyl group. The alternative ring closure involving the 5-hydroxyl group did not seem to proceed to any detectable extent, indicating that the 5-hydroxyl is unreactive, as is usually expected, owing to chelation. This observation appears to have an important bearing in regard to the mechanism of the ring isomeric change that visnagin undergoes when boiled with hydriodic acid.[12] Besides demethylation, the furan ring undergoes a shift to yield nor*iso*visnagin (VIII). This result would appear to be a contradiction of what has been mentioned above, because it could be considered to be due to the opening of only the furan ring and re-closing with the 5-hydroxyl group of the chromone. In fact the reaction seems to involve the simultaneous opening of the pyrone ring also. At this stage the furan ring closure could take place in the alternative direction, involving the 6-position of the diketone (IX), followed by re-formation of the pyrone ring.

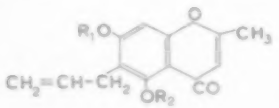


VIII



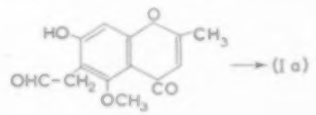
IX

By following a different sequence of the above experiments, it has been possible to obtain visnagin in much better yield. Claisen migration of the allyloxytosyloxychromone (VIc) proceeds in excellent yield. The tosyl group could not be removed from this ester (Xa) even by prolonged treatment with cold alkali. However, its 5-methyl ether (Xb), prepared readily by reaction with methyl iodide, underwent smooth detosylation to yield 2-methyl-5-methoxy-6-allyl-7-hydroxychromone (Xc).



X

(a) R_1 = Tosyl ; R_2 = H
(b) R_1 = Tosyl ; $R_2 = -CH_3$
(c) R_1 = H ; $R_2 = -CH_3$



XI

[11] A. Schönberg and N. Badran, *J. Amer. Chem. Soc.* **73**, 2960 (1951).
[12] J. R. Clark, G. Glaser and A. Robertson, *J. Chem. Soc.* 2260 (1948).

The subsequent stages of ozonolysis and ring closure of the 6-acetaldehydochromone (XI) afforded visnagin in good yield.

EXPERIMENTAL

2-Methyl-5-allyloxy-7-benzyloxychromone. On heating under reflux a solution of 2-methyl-5-hydroxy-7-benzyloxychromone[7] (3 g) in dry acetone (150 ml) containing excess of allyl bromide (3 ml) and potassium carbonate (6 g) for 35 hr, the crude allyl ether was obtained as a brown viscous liquid. Purification was effected by allowing a solution of it in benzene to percolate through a column of alumina (15 g) and eluting the column with light petroleum (400 ml, boiling range 40–60°). Evaporation of the eluate gave the allyl ether (3·2 g), which crystallised as colourless plates from dilute ethanol, m.p. 91–92° (Found: C, 74·4; H, 5·4. $C_{20}H_{18}O_4$ requires C, 74·6; H, 5·6 per cent).

2-Methyl-5-hydroxy-6-allyl-7-benzyloxychrome (IVa). The allyloxychromone (2 g) was heated under reduced pressure at 190–195° for 1½ hr. Crystallisation of the cold melt from ethanol after treatment with Norit yielded the migration product (1·9 g) as colourless needles, m.p. 129–130°, which gave a violet colour with ferric chloride (Found: C, 74·1; H, 5·8. $C_{20}H_{18}O_4$ requires C, 74·6; H, 5·6 per cent). The acetate crystallised from dilute methanol as colourless prisms m.p. 132–133°.

2-Methyl-5-methoxy-6-allyl-7-benzyloxychromone. Methylation of the 5-hydroxychromone (IVa) (0·5 g) with excess of methyl iodide and potassium carbonate (2 g) in boiling acetone (50 ml) for 50 hr yielded the methyl ether (0·5 g) as colourless prismatic rods from ethanol, m.p. 92–93° (Found: C, 74·6; H, 6·4. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0 per cent).

2-Methyl-5-hydroxy-6-(βγ-dihydroxypropyl)-7-benzyloxychromone (IVb). The acetate of 2-methyl-5-hydroxy-6-allyl-7-benzyloxychromone (0·5 g) in formic acid (10 ml) maintained at 35° was treated dropwise with an excess of 30% hydrogen peroxide (0·4 ml). After 4 hr the mixture was diluted with water, excess of peroxide was destroyed by adding a trace of 10% palladised charcoal and the solution was extracted with chloroform. The extract was washed with sodium bicarbonate solution and evaporated, and the residual glassy solid was hydrolysed by being kept in contact with 2% methanolic sodium hydroxide at 50° for 15 min. Acidification and crystallisation of the product from dilute methanol yielded the diol (0·25 g) as colourless short needles, m.p. 159–160°, which gave a violet colour with ferric chloride (Found: C, 67·6; H, 6·0. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6 per cent).

2-Methyl-5:7-dihydroxy-6-(βγ-dihydroxypropyl)chromone (Va). A methanolic solution (20 ml) of the above benzyloxychromone (250 mg) was hydrogenated in the presence of 1% palladised charcoal (250 mg) until 1 mole of the gas had been absorbed. Evaporation of the filtered solution yielded the diol (Va) (150 mg). It crystallised as colourless rhombohedral plates from dilute ethanol, m.p. 201–202°, and gave a violet colour with ferric chloride (Found: C, 58·8; H, 4·7. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3 per cent).

2-Methyl-5-hydroxy-7-benzoyloxychromone (VIa). Benzoyl chloride (5 ml) was added to a solution of 2-methyl-5:7-dihydroxychromone (5 g) in 10% aqueous sodium carbonate (200 ml) and the mixture was shaken at room temperature for 1 hr. The granular precipitate of the partial benzoate (7 g) was collected. On crystallisation from ethanol after treatment with Norit it was obtained as pale-yellow

plates, m.p. 130–131°, and it gave a violet colour with ferric chloride (Found: C, 69·0; H, 4·4. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1 per cent).

2-*Methyl*-5-*hydroxy*-7-*tosyloxychromone* (VIb). 2-Methyl-5:7-dihydroxychromone (12 g) was heated under reflux with toluene-*p*-sulphonyl chloride (14·1 g) and potassium carbonate (30 g) in dry acetone (1200 ml) for 6 hr; the tosyl ester (19·5 g) crystallised from a mixture of chloroform and ethanol as pale-yellow rectangular prisms, m.p. 141–142°, which gave a bluish-red colour with ferric chloride (Found: C, 59·1; H, 4·4. $C_{17}H_{14}O_6S$ requires C, 59·0; H, 4·0 per cent). The mother-liquor deposited, on concentration and cooling, light-yellow tablets (0·5 g) of 2-methyl-5:7-ditosyloxychromone, m.p. 130–131° (Found: C, 57·8; H, 4·1. $C_{24}H_{20}O_8S_2$ requires C, 57·6; H, 4·0 per cent).

2-*Methyl*-5-*allyloxy*-7-*tosyloxychromone* (VIc). On heating under reflux the ester (VIb) (3 g) for 8 hr with allyl bromide (3·5 ml) and potassium carbonate (10 g) in dry acetone, the ether ester (VIc) (3·5 g) was obtained, colourless prisms from ethanol, m.p. 148–149° (Found: C, 62·3; H, 5·2. $C_{20}H_{18}O_6S$ requires C, 62·2; H, 4·7 per cent).

2-*Methyl*-7-*hydroxy*-5-*allyloxychromone* (IIIb). The tosyl ester (VIc) (10 g) in ethanol (300 ml) was mixed with 5% aqueous sodium hydroxide solution (200 ml). After 4 hr at room temperature, the mixture was diluted and extracted with ether to remove any unhydrolysed ester. The clear alkaline solution was acidified and extracted with ethyl acetate, and the extract was washed twice with aqueous sodium bicarbonate solution. Concentration of the ethyl acetate solution deposited the hydroxychromone (IIIb) (5 g), which crystallised from a mixture of ethyl acetate and ethanol as colourless rectangular prisms, m.p. 202–203° (Found: C, 67·2; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2 per cent).

2-*Methyl*-5:7-*dihydroxy*-6-*allylchromone* (VIIa). When the above 5-allyloxychromone (1 g) was heated at 200–205° under reduced pressure and the cooled migration product was crystallised from ethanol after treatment with Norit the dihydroxyallylchromone (0·9 g) was obtained as colourless plates, m.p. 227–230° (Found: C, 67·5; H, 5·6. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2 per cent). It gave a violet colour with ferric chloride and a diacetate, as colourless rectangular plates from ethanol, m.p. 202–203°.

Ozonolysis of (VIIa). A stream of 3% ozonised oxygen (50 ml/min) was passed through a cooled (5°) solution of the dihydroxyallylchromone (VIIa) (300 mg) in formic acid (45 ml) for 70 min. The solution was set aside at room temperature for 1/2 hr and then stirred in an atmosphere of hydrogen in the presence of 1% palladised charcoal (0·6 g) until 1 mole of the gas had been absorbed (2 hr). The filtered and diluted solution was extracted with chloroform, and the extract was washed several times with dilute sodium bicarbonate solution and evaporated. The residual glassy solid was a mixture and could not be crystallised. It gave a positive Tollen's test and a 2:4-dinitrophenylhydrazone, which after two crystallisations from ethanol formed yellow needles, m.p. 215° (dec.) (Found: C, 52·0; H, 3·6. $C_{19}H_{14}O_8N_4$ requires C, 52·2; H, 3·4 per cent).

Cyclisation to norvisnagin (Ib). The glassy residue obtained above was treated with orthophosphoric acid (5 ml) at 100° for 10 min and then poured into cold water. The separated solid was extracted with chloroform and the extract was dried and chromatographed on a column of activated alumina (10 g). Elution of the column

with more chloroform and evaporation of the eluate yielded norvisnagin (50 mg), pale-yellow plates from ethanol, m.p. and mixed m.p. 156–157°, which gave a green colour with ferric chloride.

Further elution of the column with ethanol yielded 2-methyl-5:7-dihydroxy-6-propylchromone (60 mg), which formed colourless plates from ethyl acetate, m.p. 210–212°, undepressed by admixture with an authentic sample of the same prepared by the catalytic hydrogenation of the 6-allylchromone (VIIa) (Found: C, 67·1; H, 6·5. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0 per cent).

2-*Methyl*-5-*hydroxy*-6-*allyl*-7-*tosyloxychromone* (Xa). This was obtained by the Claisen migration of 2-methyl-5-allyloxy-7-tosyloxychromone (VIc) (1 g) at 190–195° under reduced pressure for 1½ hr; this allylchromone (0·95 g) formed colourless hexagonal plates from ethanol after treatment with Norit, m.p. 129–130°, and gave a violet colour with ferric chloride (Found: C, 62·2; H, 4·7. $C_{20}H_{18}O_6S$ requires C, 62·2; H, 4·7 per cent).

2-*Methyl*-5-*methoxy*-6-*allyl*-7-*tosyloxychromone* (Xb). Methylation of the 5-hydroxychromone (Xa) (0·9 g) by heating it under reflux with excess of methyl iodide (1 ml) and potassium carbonate (2 g) in acetone solution was complete in 16 hr. The methyl ether (0·9 g) crystallised from ethanol as colourless rectangular prisms, m.p. 111–112° (Found: C, 63·5; H, 5·1. $C_{21}H_{20}O_6S$ requires C, 63·0; H, 5·0 per cent).

2-*Methyl*-5-*methoxy*-6-*allyl*-7-*hydroxychromone* (Xc). A mixture of the above tosyl ester (0·5 g) in ethanol (30 ml) and 10% aqueous sodium hydroxide solution (30 ml) was kept at room temperature for 3 hr, diluted with water and extracted with ether to remove any unhydrolysed ester. Acidification of the clear alkaline solution yielded the 7-hydroxy-6-allylchromone (0·3 g), colourless rhombic plates from ethanol, m.p. 220–221° (Found: C, 68·2; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7 per cent).

Ozonolysis of (Xc). A stream of 2·5% ozonised oxygen (50 ml/min) was bubbled through a cooled (5°) formic acid (20 ml) solution of the hydroxyallylchromone (Xc) (300 mg) for 45 min. After the solution had been set aside for ½ hr at room temperature, it was hydrogenated in the presence of 10% palladised charcoal (0·2 g) until 1 mole of hydrogen had been absorbed. When the solvent was removed from the filtered solution by distillation under reduced pressure and the residual brownish glass was treated in ethanolic solution with 2:4-dinitrophenylhydrazine hydrochloride, the 2:4-dinitrophenylhydrazone of the 6-acetaldehydochromone (XI) was obtained as yellow needles from ethanol, m.p. 255–257° (Found: C, 52·9; H, 3·8. $C_{19}H_{16}O_8N_4$ requires C, 53·3; H, 3·8 per cent).

Cyclisation to visnagin (Ia). The crude actaldehydochromone (from 300 mg of the allylchromone (Xc)) was heated with a mixture of orthophosphoric acid (3 ml) and phosphorus pentoxide (3 g) at 100° for 20 min, and the resulting deep green solution was cooled and poured into ice–water. The light-brown solid that separated was extracted with benzene, and the extract was dried and allowed to percolate through a short column of alumina (3 g); the column was then washed with more benzene. Evaporation of the eluate and the washings yielded visnagin (200 mg), m.p. and mixed m.p. 139–140°.

Tetrahedron, 1958, Vol. 3, pp 236–242. Pergamon Press Ltd., London

NAPHTHAQUINONES—I

THE MOLECULAR STRUCTURES OF SOME HALOGENO-2:7-DIHYDROXYNAPHTHALENES

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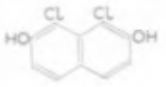
(*Received* 14 *January* 1958)

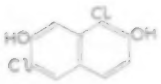
Abstract—Some new substituted naphthaquinones have been prepared by the oxidation of derivatives of 2:7-dimethoxynaphthalene with chromic acid. From an examination of the experimental results recorded in this paper and of some already available in the literature, it is now concluded that monobromination of 2:7-dihydroxynaphthalene gives the 1-bromo derivative and that dibromination and dichlorination furnish the 1:6-dibromo and 1:6-dichloro compounds.

IT has previously been shown[1,2] that the dibromination and dichlorination of 2:7-dihydroxynaphthalene give either 3:6-dibromo- and 1:8-dichloro-2:7-dihydroxynaphthalene (I, II) or the 1:6-dihalogeno derivatives (III, IV). Dibromination of the



(I)

(II)



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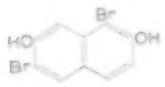
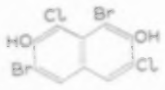
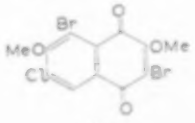


(IV)

dichloro-2:7-dihydroxynaphthalene was found to yield the same product as dichlorination of the dibromodiol. The absence of an atom of halogen in the 4-position (and in the 5-position, on the basis of the expected symmetry) is implied from the preparation of the yellow compound, 3:8-dibromo-6-chloro-2:7-dimethoxy-1:4-naphthaquinone (VI), by the oxidation, with chromic acid in acetic acid, of the dimethyl ether of



(V)



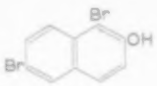
(VI)

the tetrahalogenodiol. The latter compound is now thought to be represented by the formula (V). It may be noted that, despite the lack of activation of the 4-carbon atom

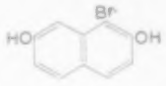
[1] F. Bell, J. A. Gibson and R. D. Wilson, *J. Chem. Soc.* 2335 (1956).
[2] R. D. Wilson, Thesis for the Fellowship of the Heriot-Watt College, Edinburgh (1957).

by the hydroxyl group,[3] 1-chloro-2-naphthol yields, on chlorination, the 1:4-dichloro compound,[4,5] through the decomposition of an addition compound.

There will be discussed the significance of the experiments of some other workers in relation to the structure of the monobromo-2:7-dihydroxynaphthalene and hence to the molecular configurations of other halogeno derivatives of the diol. The preparations of various naphthaquinones described in this paper will then be shown to provide support for the contention[2] that the dichlorination and dibromination of 2:7-dihydroxynaphthalene both yield products (III, IV) that are analogous to the compound (VII) from the dibromination of 2-naphthol.[6,7]



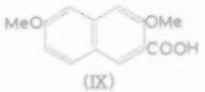
(VII)



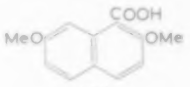
(VIII)

Discussion of molecular structures of some halogeno-2:7-dihydroxynaphthalenes and their methyl ethers

It is necessary as a preliminary to emphasise certain facts. First, the products of the mono-, di- and tri-bromination of 2:7-dimethoxynaphthalene are identical with the dimethyl ethers formed from the mono-, di- and tri-bromo-2:7-diols (VIII, IV and XVI), respectively (see Bell *et al.*[1] and under "Experimental"). It follows then that the mono-, di- and tri-bromination of 2:7-dihydroxynaphthalene give products that are structurally similar to those from the corresponding halogenations of the dimethyl ether, assuming that no quite unexpected rearrangement occurs during etherification. Secondly, the molecular structures of two 2:7-dimethoxynaphthoic acids are known. Sunthankar and Gilman[8] made the 3-naphthoic acid (IX) by acidification of the



(IX)

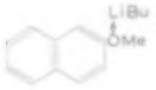


(X)

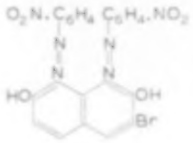
product of carbonation of the lithio derivative of 2:7-dimethoxynaphthalene. The structure of this acid, also obtained by Buu-Hoï and Lavit[9] by the oxidation of 3-acetyl-2:7-dimethoxynaphthalene, obtained from the Friedel–Crafts acetylation of the dimethoxynaphthalene, was determined by demethylation to the dihydroxynaphthoic acid. The latter had been prepared by Schmid,[10] who considered it was the 3-naphthoic acid in view of the difficulty of decarboxylation. Sunthankar and Gilman gave further support for this structure by obtaining, from 2:7-dimethoxynaphthalene by their general method of using lithio compounds, a 2:7-dihydroxynaphthalenedicarboxylic acid, one molecule of which coupled with two molecules of diazotised sulphanilamide. The other 2:7-dimethoxynaphthoic acid, afforded by the oxidation of the corresponding

[3] M. J. S. Dewar, *The Electronic Theory of Organic Chemistry* p. 175. Oxford University Press, Oxford (1949).
[4] P. M. James and D. Woodcock, *J. Chem. Soc.* 1931 (1951).
[5] P. W. Robertson, *J. Chem. Soc.* 1883 (1956).
[6] A. J. Smith, *J. Chem. Soc.* **35**, 789 (1879).
[7] H. E. Armstrong and E. C. Rossiter, *Proc. Chem. Soc.* **5**, 71 (1889).
[8] S. V. Sunthankar and H. Gilman, *J. Org. Chem.* **16**, 8 (1951).
[9] Ng. Ph. Buu-Hoï and D. Lavit, *J. Chem. Soc.* 1743 (1956).
[10] J. Schmid, *Ber. Dtsch. Chem. Ges.* **26**, 1114 (1893).

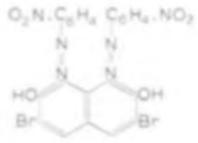
naphthaldehyde,[9,11] must therefore have the formula (X). The aldehyde, prepared by the methylation of the product of a Gattermann synthesis using the 2:7-diol[11] or by formylation of 2:7-dimethoxynaphthalene with dimethylformamide and phosphorus oxychloride,[12] would be expected to have the formyl group (of small effective bulk) on the 1-carbon atom. On the other hand, as pointed out by Sunthankar and Gilman, the formation of a lithio compound probably involves an intermediate co-ordination complex (XI), from the 3-position of which a proton is removed by nucleophilic attack by a carbanion from the reagent, *n*-butyl-lithium. There follows the attaching of a lithium cation to the 3-carbon atom.



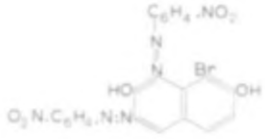
(XI)



(XII)



(XIII)



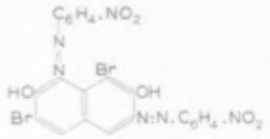
(XIV)

Now Adams *et al.*[11] obtained the 1-naphthoic acid (X) from the bromo 2:7-dimethoxynaphthalene by the action of *n*-butyl-lithium, followed by carbonation and treatment with hydrochloric acid. Thus it is proved that the product of the monobromination of 2:7-dihydroxynaphthalene must be the 1-bromo compound (VIII). Since the dibromo derivative has been shown to be either 1:6- or 3:6-dibromo-2:7-dihydroxynaphthalene,[1] it must now be concluded that it is actually the former (IV). From the earlier remarks 2:7-dimethoxynaphthalene must similarly yield the 1-bromo and 1:6-dibromo derivatives. In view of the recognised marked reactivity of the 1- and 8-positions in 2:7-dihydroxynaphthalene owing to electronic factors,[3] the entry of the second bromine atom into the 6-position is attributed to steric hindrance.

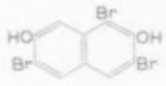
The only experimental work that does not at once appear to confirm these conclusions is due to Ioffe and Fedorova.[13] They found that one molecule of the bromo-2:7-diol or of the dibromo compound coupled with two molecules of diazotised *p*-nitroaniline, and they believed the products were the compounds (XII) and (XIII), respectively. Their results are, however, open to various other interpretations. For example, it is possible that coupling, involving an electrophilic attack,[14] takes place in the 6- and 8-positions in the monobromodiol and at the 3- and 8-carbon atoms in the dibromo compound, to give the products (XIV) and (XV), despite the known inertness of the 3-position in 1-methyl-2-naphthol[3] and the displacement of a bromine atom from the 1-carbon atom on treating 1-bromo-2-naphthol with diazotised *p*-nitroaniline. It is worthy of note that the primary isolable product in this last

[11] R. Adams, M. W. Miller, F. C. McGrew and A. W. Anderson, *J. Amer. Chem. Soc.* **64**, 1795 (1942).
[13] Ng. Ph. Buu-Hoï and D. Lavit, *J. Chem. Soc.* 2776 (1955).
[13] I. S. Ioffe and N. M. Fedorova, *J. Gen. Chem., U.S.S.R.* **6**, 1079 (1936); *Chem. Abstr.* **31**, 1022 (1937).
[14] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 297. Bell, London (1953).

reaction is probably the *p*-nitrobenzenediazo ether of 1-bromo-2-naphthol (XXII).[15,16] The coupling reactions are being further investigated experimentally. Ioffe and Fedorova made also the tribromodiol, the structure of which was indicated by the formula (XVI). This agrees with the present conclusions, when steric hindrance to substitution in the 8-position is considered.



(XV)



(XVI)

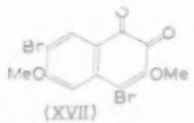
From the opening remarks in the introduction to this paper it is seen that the dichloro- and the dibromodichloro-2:7-dihydroxynaphtahlenes have the formulae (III) and (V), respectively. The dimethyl ethers corresponding to these halogenated diols (XVI, III and V) must have analogous structures.

Adams and his colleagues[11] were seeking optical activity due to the restricted rotation of groups in the *peri*-positions of derivatives of naphthalene. Their lack of success may be explained on the basis of the foregoing discussion. For example, it now seems that the compound, to which they ascribed the formula (XXIII), is correctly represented by the structure (XXIV) (cf. Bell *et al.*[1]).

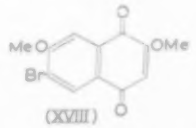
Confirmation of the molecular structures of some halogeno-2:7-dihydroxynaphthalenes by the preparation of quinones

From 2:7-dimethoxynaphthalene was obtained the yellow-orange 1:4-quinone, made by Fieser and Brown from ammonium 7-methoxy-1:2-naphthaquinone-4-sulphonate.[17]

The oxidation of the dibromo-2:7-dimethoxynaphthalene afforded a maroon and a yellow product. The colour of the former is indicative of an *o*-quinone, whilst that of the latter is characteristic of a *p*-quinone.[18] The analytical results for the maroon compound correspond to a dibromodimethoxynaphthaquinone, and the other compound appears to be a monobromodimethoxynaphthaquinone. Now these results are compatible with the representation of the dibromodiol by the formula (IV), but not by the formula (II). An *amphi*-quinone containing both of the methoxy groups is clearly impossible. Thus the products of oxidation have the structures (XVII) and (XVIII).



(XVII)

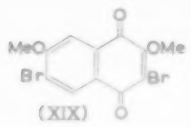


(XVIII)

The tribromo-2:7-dimethoxynaphthalene yielded a yellow quinone, isomeric with, but different from, the dibromoquinone (XVII) obtained by the oxidation of the dibromodimethoxynaphthalene. The sole reasonable structure for this new quinone

[15] J. Pollak and E. Gebauer-Fülnegg, *Anz. Akad. Wiss. Wien* **63**, 145 (1927); *Chem. Abstr.* **22**, 3651 (1928).
[16] J. Pollak and E. Gebauer-Fülnegg, *Mh. Chem.* **50**, 310 (1928).
[17] L. F. Fieser and R. H. Brown, *J. Amer. Chem. Soc.* **71**, 3615 (1949).
[18] E. Cerutti and J. Martinet, *C. R. Acad. Sci., Paris* **237**, 1336 (1953).

is given by the formula (XIX), which is consistent with attributing to the tribromo-2:7-dihydroxynaphthalene the formula (XVI), proposed both by Ioffe and Fedorova and by the present author. It is to be noted, however, that this structure is precisely that for the only possible dibromodimethoxynaphthaquinone from the oxidation of the dibromodimethoxynaphthalene corresponding to the structure (II) advocated by Ioffe and Fedorova for the dibromodiol.



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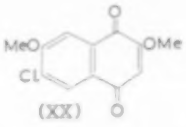
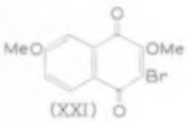


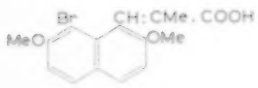
(XX)

From the oxidation of the dichloro-2:7-dimethoxynaphthalene has been isolated only a yellow compound, containing one atom of chlorine in its molecule. This product, from a consideration of the result of the oxidation of the bromo analogue, is given the formula (XX). Although it is true that the analytical results for this compound (XX) do not preclude the representation of the dichlorodiol by Clausius's formula (I),[19] this is opposed by the fact that the dibromodiol does not have the structure (II) and yet on dichlorination it yields the same compound as that obtained by the dibromination of the dichloro-2:7-dihydroxynaphthalene (see introduction to this paper).

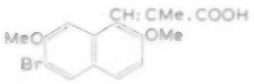


(XXI)

(XXII)



(XXIII)



(XXIV)

Note added in proof: The author has overlooked a communication by Cooke, Johnson and Owen,[20] who have submitted experimental evidence that the major product of the dibromination of 2:7-dihydroxynaphthalene is the 1:6-derivative (m.p. 162–163°). They have prepared also 3-bromo-2:7-dihydroxynaphthalene (m.p. 191–192°). The only monobromo-derivative that has previously been described[1,18] is 1-bromo-2:7-dihydroxynaphthalene (m.p. 135°), the structure of which is discussed above.

EXPERIMENTAL*

2:7-*Dimethoxynaphthalene*. This ether was prepared in the normal way, by shaking dimethyl sulphate with a solution of the diol in aqueous sodium hydroxide. Light

* Melting points are uncorrected for the emergent column.

[19] A. Clausius, *Ber. Dtsch. Chem. Ges.* **23**, 517 (1890).

[20] R. G. Cooke, B. L. Johnson and W. R. Owen, *Chem. & Ind.* 1623 (1957).

cream-coloured needles, m.p. 138° (67 per cent of theoretical yield), were obtained by recrystallisation from acetic acid. A second crop of crystals (5 per cent of theoretical yield) melted at 135–136° (138°[21]).

2:7-*Dimethoxy*-1:4-*naphthaquinone*. To a solution (at 20°) of 2:7-dimethoxynaphthalene (5·51 g) in acetic acid (250 ml) was added in small portions during 3 hr, a solution (at 20°) of chromium trioxide (24·4 g) in water (53 ml). The heat of reaction gave a maximum temperature of 43° during the mixing. After being left for 24 hr, the product was heated to 40° for 30 min, cooled and poured into water (3·5 l.). The precipitate (1·31 g), after being washed with water and dried, melted at 212°. Crystallisation from acetic acid afforded small yellow-orange needles, m.p. 215° (Found: C, 65·7; H, 4·8. Calc. for $C_{12}H_{10}O_4$: C, 66·0; H, 4·6 per cent). Fieser and Brown,[17] who prepared this compound by a different method, recorded a m.p. of 214–215°.

3-*Bromo*-2:7-*dimethoxy*-1:4-*naphthaquinone* (XXI). A solution of bromine (0·16 ml) in acetic acid (25 ml) was added during 20 min to 2:7-dimethoxy-1:4-naphthaquinone (0·57 g) in the same solvent (13 ml). The mixture was then kept at 60–80° for 30 min before it was poured into water (500 ml). The precipitate (0·65 g) melted at 132–134°. Crystallisation from acetic acid gave minute orange needles of the *bromo derivative*, m.p. 136·5° (Found: C, 48·5; H, 3·1; Br, 26·8. $C_{12}H_9O_4Br$ requires C, 48·5; H, 3·1; Br, 26·9 per cent). The use of twice the above-mentioned proportion of bromine gave a smaller yield of 3-bromo-2:7-dimethoxy-1:4-naphthaquinone as the only isolable product. In connexion with the ascribed structure (XXI), it may be mentioned that treatment of 5:8-dihydroxy-1:4-naphthaquinone with bromine afforded the 2-bromo derivative.[22]

1:6-*Dibromo*-2:7-*dimethoxynaphthalene*. A solution of bromine (4·7 g) in acetic acid (10 ml) was poured into a solution of 2:7-dimethoxynaphthalene (2·60 g) in the same solvent (65 ml). After 24 hr the precipitated needles were filtered off and washed with acetic acid. The dry light-grey product (3·38 g) melted at 129–130° (131° in lit.[1], where the compound is designated as "2:7-dibromo-3:6-dimethoxynaphthalene").

Oxidation of 1:6-*dibromo*-2:7-*dimethoxynaphthalene*. A solution (at 15°) of chromium trioxide (2·27 g) in water (3·5 ml) was added to a solution (at 50°) of 1:6-dibromo-2:7-dimethoxynaphthalene (2·06 g) in acetic acid (50 ml). After 1 hr the mixture was poured into water (300 ml). After being washed with water and dried, the dark-red precipitate (0·60 g) was treated with acetic acid at 100°. Filtration of the hot product gave a maroon residue (A). From the cold filtrate was deposited a solid, which was filtered off and washed with acetic acid, to yield a yellow-brown residue (B).

The substance (A) was recrystallised from benzene, to give minute maroon needles of 4:7-*dibromo*-3:6 *dimethoxy*-1:2-*naphthaquinone* (XVII), m.p. 230° (Found: C, 38·6; H, 1·9. $C_{12}H_8O_4Br_2$ requires C, 38·3; H, 2·1 per cent).

Recrystallisation of the residue (B) from acetic acid furnished very small yellow needles of 6-*bromo*-2:7-*dimethoxy*-1:4-*naphthaquinone* (XVIII), m.p. 256–258° (Found: C, 47·9; H, 3·5; Br, 27·4. $C_{12}H_9O_4Br$ requires C, 48·5; H, 3·1; Br, 26·9 per cent).

An attempt was made to use *n*-butyric acid[23] as the solvent for oxidation by chromium trioxide, but the only compound isolated from the mixture was unchanged 1:6-dibromo-2:7-dimethoxynaphthalene.

[21] S. N. Chakravarti and V. Pasupati, *J. Chem. Soc.* 1859 (1937).
[22] L. Brüll and P. Girotti, *Ann. Chim. Appl.* **26**, 19 (1936).
[23] R. D. Wilson, *Chem. & Ind.* 758 (1957).

1:3:6-*Tribromo*-2:7-*dimethoxynaphthalene*. To a solution of 2:7-dimethoxynaphthalene (18·9 g) in acetic acid (600 ml) was added bromine (16·3 ml) in acetic acid (200 ml) in small portions during 50 min. The mixture was then kept at 100° for 2 hr. Cooling and subsequent filtration yielded light-grey needles (15·7 g), m.p. 164–167°. Dilution of the mother-liquor with water (1 l.) precipitated more solid (22 g; greenish brown).

The solid with m.p. of 164–167° was recrystallised from acetic acid and then from ethanol, to give minute white needles, m.p. 172·5°. 1:3:6-Tribromo-2:7-dimethoxynaphthalene, prepared by methylating the tribromodiol, melted[1] at 173°.

2:7-*Dibromo*-3:6-*dimethoxy*-1:4-*naphthaquinone* (XIX). To 1:3:6-tribromo-2:7-dimethoxynaphthalene (5·55 g) in acetic acid (200 ml) was slowly added, in small portions, a solution of chromium trioxide (10·5 g) in water (23 ml). The maximum temperature of the product during the mixing was 22°. The mixture was then kept at 50° for 1 hr, cooled and filtered, to give a grey residue (0·5 g). The filtrate was poured into water (1·5 l.) to yield a precipitate, from which, by repeated crystallisation from acetic acid, were obtained very small yellow needles of 2:7-*dibromo*-3:6-*dimethoxy*-1:4-*naphthaquinone* (XIX), m.p. 212·5–213·5° (Found: C, 38·5; H, 2·0. $C_{12}H_8O_4Br_2$ requires C, 38·3; H, 2·1 per cent).

The use of one-half of the above proportion of chromium trioxide afforded a considerable yield of unchanged tribromodimethoxynaphthalene, while attempted oxidation with potassium permanganate in AnalaR acetone led to the recovery of 87 per cent of the original tribromodimethoxynaphthalene.

1:6-*Dichloro*-2:7-*dimethoxynaphthalene*. Sulphuryl chloride (5·7 ml) was added cautiously to 2:7-dimethoxynaphthalene (6·1 g) in chloroform (10 ml). The mixture was heated under reflux for 30 min, cooled and filtered. Concentration of the filtrate yielded a dark brown substance, which was discarded. The residue, after being washed with a small quantity of chloroform, weighed 3·4 g and melted at 140–143°. Recrystallisation from acetic acid gave white prisms of 1:6-*dichloro*-2:7-*dimethoxynaphthalene*, m.p. 143–143·5° (Found: C, 56·9; H, 4·1; Cl, 27·2. $C_{12}H_{10}O_2Cl_2$ requires C, 56·1; H, 3·9; Cl, 27·6 per cent).

6-*Chloro*-2:7-*dimethoxy*-1:4-*naphthaquinone* (XX). A solution (at 15°) of chromium trioxide (5·5 g) in water (14 ml) was run, during 5 min, into 1:6-dichloro-2:7-dimethoxynaphthalene (2·82 g) in acetic acid (70 ml) at 50°. After 1 hr the product was diluted with water (700 ml). The isolated precipitate (0·41 g) was recrystallised twice from a filtered solution in hot acetic acid. Sublimation of the product afforded yellow-orange needles of 6-*chloro*-2:7-*dimethoxy*-1:4-*naphthaquinone* (XX), m.p. 280–282° (Found: C, 56·6, 56·6; H, 3·6, 3·5; Cl, 14·4. $C_{12}H_9O_4Cl$ requires C, 57·0; H, 3·6; Cl, 14·0 per cent).

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C-22 KETALS RELATED TO THE SAPOGENINS*

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(*Received* 21 *January* 1958)

Abstract—Reduction of 5,6-dihydrokryptogenin diacetate with Raney nickel in ethanol reduced the 16-ketone group and gave a mixture of a 22-ethyl ketal with a hemiketal. Both undergo elimination reactions very readily to yield the Δ^{22}-bond isomer of pseudotigogenin diacetate. The conversions are reversible and are catalyzed by acetic acid and in neutral solution by calcium sulfate and other surfaces. Alkaline hydrolysis followed by cyclization with acetic acid converted both the ketal and the Δ^{22}-olefin to tigogenin. The relative stabilities of ketal epimers at C-22 are discussed and related to the stereochemistry of the sapogenins and the *cyclo*pseudosapogenins.

THREE years ago an attempt was made to deduce the configuration of the sapogenins at C-22 by conformational analysis.[1] In the case of the sapogenins which belong to the so-called *iso* series, an unambiguous selection seemed possible that agreed with that preferred for various reasons also by other workers.† In the normal series only a tentative conclusion was drawn. The chief uncertainty was whether the difference (*A*) in interactions that would result from an interchange of the axial and equatorial substituents at C-25 would exceed the difference (*B*) in the eclipsed interactions of the substituents at C-20 and C-22 that would result from an interchange of the C-23 methylene and the pyranoid oxygen. On the basis of Pitzer's estimates of the rotational barriers of propane and butane we suggested that (*A*) was larger than (*B*). Since that time, Dauben and Pitzer[3a] have raised the original estimate for butane from 3600 to a value of 4400 to 6100 cal and state that no reliable calculation has been possible. This revision invalidated our argument that the *normal* and *iso*sapogenins differ in their configuration at C-22.

Before this development we had started a study of model substances related to the sapogenins in order to obtain a better estimate of (*B*). While this work was in progress two important communications appeared which bear on this problem. Callow and Massy-Beresford[4] have related sapogenins of the *normal* and of the *iso* series by reactions designed not to change the configuration at C-22 and have concluded that both series possess identical configurations at this asymmetric center and differ in their conformations at C-25. This result is to be expected if (*A*) is smaller than (*B*).

* Supported by grant C-1679 of the National Institutes of Health, U.S. Public Health Service.

† For review of the earlier literature see Hirschmann *et al.*[1] The assignment originally made by Wall and Serota was revised.[2]

[1] H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *J. Org. Chem.* **20**, 572 (1955).

[2] M. E. Wall, S. Serota and C. R. Eddy, *J. Amer. Chem. Soc.* **77**, 1230 (1955).

[3] M. S. Newman, *Steric Effects in Organic Chemistry*. Wiley, New York (1956): [3a] W. G. Dauben and K. S. Pitzer, *Op. cit.* pp. 8, 15 and 24; [3b] D. J. Cram, *Op. cit.* p. 304; [3c] F. H. Westheimer, *Op. cit.* p. 533.

[4] R. K. Callow and P. N. Massy-Beresford, *Chem. & Ind.* 1146 (1956); *J. Chem. Soc.* 4482 (1957).

On the other hand, Wall and Walens[5] have presented evidence in support of the thesis[6] that *cyclo*pseudosapogenins of the two series differ in their configurations at C-22 and agree in their conformations at C-25. This leads to the conclusion that (*A*) is larger than (*B*). In view of this apparent contradiction,* it seems of interest to report our findings on monocylic C-22 ketals, such as (III), since their stability should no longer be dependent on their configuration at C-25.

A possible route to such compounds was suggested by the work of Kaufmann and Rosenkranz,[7] who reduced kryptogenin and its diacetate with Raney nickel in alcohol and observed selective reduction of the 16-keto group. The resulting free compound, which occurs as a hemiketal at least in the crystalline state,[8] readily cyclized with acid to form diosgenin.[7] The amorphous diacetate gave pseudodiosgenin diacetate on treatment with phosphorus oxychloride and pyridine as well as on boiling with tetrahydronaphthalene or acetic anhydride. This suggested a hemiketal structure also for the diacetate. With a view to studying the relative stabilities of the two isomers permitted by asymmetry at C-22, we repeated the reduction of kryptogenin diacetate.

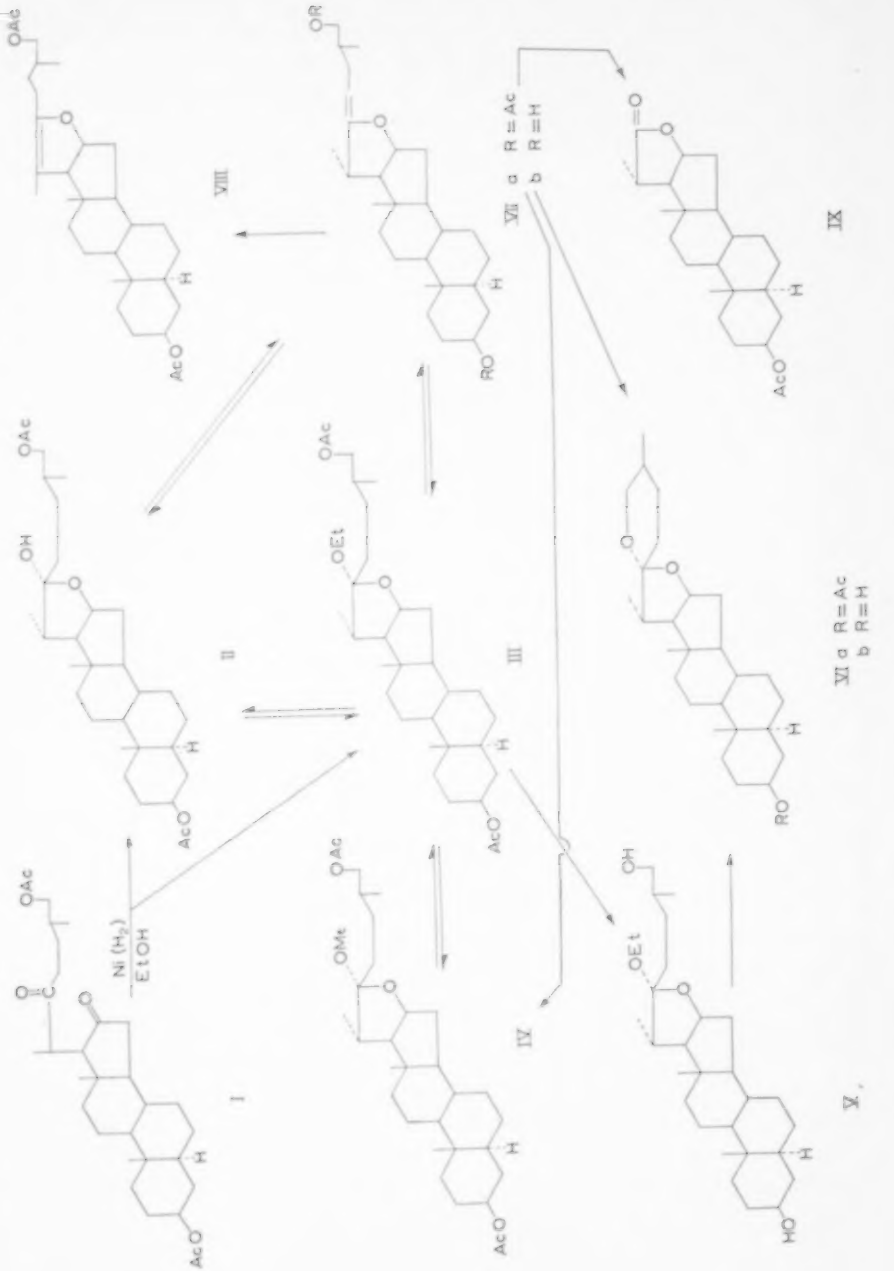
Our reduction product, which no longer possessed the absorption band at 5·82 μ of the 22-ketone group,† proved to be a mixture which could be separated by crystallization into a hydroxylic and non-hydroxylic component. Completely analogous results were obtained in the reduction of 5,6-dihydrokryptogenin diacetate (I). The two reduction products (II) and (III) were closely related. The hydroxylated compound (II) yielded the non-hydroxylic product (III) in the presence of ethanol and acetic acid at room temperature, while dilute acetic acid reversed this process. Compound (III) gave a new substance (IV) with methanol and acetic acid, which reverted to the starting compound with ethanol and acetic acid. All three products (II), (III) and (IV) showed maxima at 5·77 and 8·08 μ of such intensity as to indicate the presence of two acetoxy groups but had no other carbonyl peak. The origin of these compounds and their very facile interconversions in the presence of acid suggested that they represented a hemiketal and an ethyl and a methyl ketal, respectively. Their composition was consistent with this view, which received further support from the conversion of (III) to tigogenin (VIb) by alkaline hydrolysis and cyclization in alcoholic acetic acid. This demonstrated that only the carbonyl group at C-16 had been reduced by the nickel hydrogenation of compound (I), while the one at C-22 had been masked by derivatization.

Attempts to chromatograph either the original reduction mixture or the pure ketal (III) on silica gel–Celite led to the destruction of the ketal and yielded mixtures

* This conflict was not recognized by Wall,[6] who rationalized the different assignments for the *cyclo*pseudosapogenins ("20 β-series") as follows: "A different situation occurs in the 20 β-series. In this case the C_{21} methyl is replaced by a much smaller hydrogen atom, and models show no interaction in either of the two C_{22} possibilities." While this analysis described the situation to the rear of ring E, it took no account of the replacement of a hydrogen by the much larger methyl on the frontal side.

† Our measurement for kryptogenin diacetate agrees with reports on this[9] and other[9] 16-substituted 22-ketones, but differs from observations[10] for 22-monoketones which were found to absorb near 5·87 μ.

[5] M. E. Wall and H. A. Walens, *Chem. & Ind.* 818 (1957).
[6] M. E. Wall, *Experientia* **11**, 340 (1955).
[7] S. Kaufmann and G. Rosenkranz, *J. Amer. Chem. Soc.* **70**, 3502 (1948).
[8] R. S. Miner and E. S. Wallis, *J. Org. Chem.* **21**, 715 (1956).
[9] C. R. Eddy, M. E. Wall and M. K. Scott, *Analyt. Chem.* **25**, 266 (1953).
[10] W. Tarpley and C. Vitiello, *Appl. Spectroscopy* **9**, 69 (1955). I. Scheer, M. J. Thompson and E. Mosettig, *J. Amer. Chem. Soc.* **79**, 3218 (1957).


OAc
O
H
AcO
I
Ni (H2)
EtOH
II
OH
III
OEt
IV
OMe
V
HO
VI a R=Ac
b R=H
RO
VII a R=Ac
b R=H
VIII
OR
IX
=O

containing the hemiketal (II) and an amorphous product (VIIa), characterized by an absorption band of the same wavelength (5·91 μ) and similar intensity as the double-bond stretching band of the vinyl ether group in pseudotigogenin diacetate (VIII).[11] Like pseudotigogenin,[12] (VIIa) was not altered by hydrogenation with platinum in a neutral solvent. On the other hand, (VIIa) differed from pseudotigogenin diacetate not only in several bands in the finger-print region of the infrared spectrum (Table 1), but also in its chemical behavior. On treatment with ethanol and acetic acid (VIIa) furnished the ethyl ketal (III), while pseudotigogenin diacetate was recovered unchanged. Alkaline hydrolysis of (VIIa) gave the crystalline parent compound (VIIb), which was converted to tigogenin (VIb) in ethanolic acetic acid. Pseudotigogenin with methanolic* acetic acid[13] yielded an isomer, *cyclo*pseudotigogenin. Oxidation of (VIIa) with chromic acid gave the known[14] 3β-acetoxy-16β-hydroxybisnor*allo*-cholanic 22 → 16-lactone (IX) as the main product. These observations show that the new vinyl ether (VIIa) is the Δ^{22}-bond isomer of pseudotigogenin diacetate and make it very probable that the C-21 methyl in (VIIa) as well as in the ketals and the hemiketal is directed towards the rear just as it is in the reaction products (VI) and (IX).[15] The position of the double bond admits the possibility of *cis–trans* isomerism. We are uncertain whether our preparations represent a single geometric isomer, since the instability of (VIIa) interfered with attempts towards its fractionation. Chromatography on silica gel–Celite led to contamination with the hemiketal (II) and drastic spectral changes occurred even on standing evidently owing to autoxidation.

The marked differences in the spectra of (VIIa) and (VIII) permitted their use as a diagnostic tool in following the course of eliminations at C-22. Treatment of the ethyl ketal (III) with a mixture of benzene and acetic acid at room temperature caused desaturation and gave the Δ^{22}-isomer, while boiling in ethanol and acetic acid furnished slowly the *endo*cyclic olefin. The greater stability of this isomer could be demonstrated also at room temperature by a conversion of (VIIa) to (VIII) in the presence of acetic and phosphoric acids. The *exo*cyclic product was obtained when benzene solutions of (III) were shaken with Drierite (anhydrous calcium sulfate). The process can be reversed in alcoholic solution and requires rather large amounts of the catalyst. Complete eliminations occurred more readily with the hemiketal and gave compound (VIIa) of good spectral purity. The reactions catalyzed by Drierite are probably mechanistically distinct from those proceeding with acid, since our preparation of calcium sulfate, when suspended in water, acted as an acceptor rather than a donor of hydrogen ions. The process was viewed as surface catalysis and was expected to show a preference for *cis* elimination to yield the more stable isomer, whereas the acid-catalyzed reaction normally favors the formation of the more stable product by *trans* elimination.[3b] Since our reactions when conducted under the mildest conditions gave the less stable isomer by both modes of elimination, the result probably does not reflect the relative positions of the ethoxy group to the hydrogen at C-20, but rather suggests that the abstraction of this hydrogen is retarded by steric hindrance. There is good

* Ethanol has been used with other pseudosapogenins.[3]

[11] A. L. Hayden, P. B. Smeltzer and I. Scheer, *Analyt. Chem.* **26**, 550 (1954).
[12] R. K. Callow, D. H. W. Dickson, J. Elks, R. M. Evans, V. H. T. James, A. G. Long, J. F. Oughton and J. E. Page, *J. Chem. Soc.* 1966 (1955).
[13] M. E. Wall and H. A. Walens, *J. Amer. Chem. Soc.* **77**, 5661 (1955).
[14] R. Tschesche and A. Hagedorn, *Ber. Dtsch. Chem. Ges.* **68**, 1412 (1935).
[15] J. W. Corcoran and H. Hirschmann, *J. Amer. Chem. Soc.* **78**, 2325 (1956).

TABLE 1. INFRARED ABSORPTION MAXIMA BETWEEN 7·55 AND 11·25 μ*

Compound	Wavelength (μ)																
(II)				8·50	8·68	8·82	9·09	9·32^b		**9·74**	10·06^i	**10·19**	**10·30**	10·42^i	10·64^b	10·89^b	11·17
(III)			8·43	8·54	8·67	8·82	**9·02**		**9·41**	**9·75**	10·03	**10·20**^{b}		10·42		10·87	11·16
(IV)			8·36	8·54	8·67	8·82	**9·08**		**9·38**	**9·75**	10·01^i	10·21^i		10·42	10·63^b	10·92^b	11·21
(VIa)		7·71		**8·52**	8·66	8·84	9·11	**9·31**	**9·49**	**9·76**	10·06	**10·19**		**10·42**		**10·85**	**11·12**
				G	H	J	K		N					R			
(VIIa)	7·64	7·73		**8·54**	8·66	8·83		9·27		**9·73**	10·07	10·18		**10·40**	10·61	10·94^b	11·17
(VIII)		7·69	8·42	8·59	8·67	8·83	9·01	9·28		**9·69**		10·17		10·43^b	10·62		11·16

* Solvent was carbon disulfide. The following are omitted from this Table. Very weak maxima and inflexions, the strong ester peaks at 8·06 μ in (VIa) and at 8·08 μ in the other compounds, as well as the peak of (VIa) at 9·93 μ and the inflexions of (III) at 9·85, of (IV) at 9·85 and 9·95, of (VIa) at 9·24 and 10·50, of (VIIa) at 8·20, and of (VIII) at 8·22 and 9·83 μ. i = inflexion. b = broad. Strong bands are in bold face type. The capital letters refer to the band designations of R.N. Jones, E. Katzenellenbogen and K. Dobriner, (*J. Amer. Chem. Soc.* **75**, 158 (1953), for *iso*sapogenins but list only those which occur in the spectra of both (III) and (IV) with intensity and position comparable to those in (VIa). Absorption frequencies and a curve have been published for (VIa) by Eddy *et al.*[8] and a curve for (VIII) by Callow *et al.*[12]

evidence that an external* base is restrained from supporting the ionization of hydrogen at the frontal face of C-20, because the reverse process, the protonation of the $\Delta^{20(22)}$ double bond of pseudosapogenin, proceeds much faster from the rear, although the product, *cyclo*pseudosapogenin,† is less stable than the one resulting from frontal protonation (VIb). Therefore the formation of the *exo*cyclic isomer in an ionic process does not prove a *cis* relationship of the ethoxy group to the hydrogen at C-20.

The only elimination mechanism which would avoid complications from steric hindrance effects appears to be a unimolecular pyrolysis.[16] It could not be realized with our substrate. The results of pyrolyses of compound (III), which were conducted in evacuated tubes without solvent, depended on the surface of the vessel. Clean glass tubes gave mixtures of the two olefins in which the *exo*cyclic isomer generally predominated. As the reaction temperature was lowered from 195° to 158°, the elimination of alcohol became increasingly incomplete and reversible. This suggested surface catalysis of the elimination. Other workers[16,17] have observed such catalysis repeatedly and were able to prevent it by coating the wall with a carbonaceous residue. Pyrolysis of (III) at 158° in tubes pretreated by exposure to hot ethylene[17] went to completion and gave the *endo*cyclic isomer. However, this need not have been the primary reaction product, since (VIIa) under the same conditions was isomerized to (VIII). Finally a silvered tube gave (VIIa) as the sole olefinic product. The reaction at 158° could not be carried to completion by lengthening the reaction time, but its apparent end-point did not constitute a true equilibrium, since treatment of the pyrolysis product with a large excess of ethanol caused only a moderate increase in (III). Evidently the silver-lined surface likewise participated in the elimination.

In the presence of acetic acid ketals could be formed from other full or half ketals or from the Δ^{22}-olefin. Since the latter was obtained with the same catalyst from ketals in a medium free of hydroxylic compounds, it is possible that the ketal exchange involves the olefin as an intermediate. However, regardless of the mechanism, the main steric effects should be those governing the reaction at C-22, since it is close to the C-21 methyl, while a trigonal C-23 appears to be about equally accessible from either side. If the steric result depends on the degree of steric hindrance towards the approach of the alcohol, the faster reaction should be the one from the front to yield a product in which the C-23 methylene is eclipsed by the C-21 methyl. As pointed out before,[1] this is the less stable isomer. The compound actually isolated from the reaction must have the stable configuration. The ethyl ketal in methanol and acetic acid is converted completely to the methyl ketal in less than 10 min, but undergoes no spectrographic changes in ethanol and acetic acid when kept for a period twenty times as long. Even after boiling, no isomer of (III) could be detected. Another indication for the stable configuration of the ketals is the addition or exchange reaction involving an alcohol function at C-26. The reactions proceed at room temperature under the same conditions; the same considerations as to the probable mechanism of the faster

* The hydrogen at C-23 is also more accessible to an internal base such as the furanoid oxygen or the C-26 acetoxy group if these should play a role in the elimination. (Cf. R. T. Arnold, *Helv. Chim. Acta* **32**, 134 (1949).)

† This configuration at C-20, which was first proposed by Wall and co-workers, has been accepted by most investigators. An additional argument in its favor will be given below.

[16] D. H. R. Barton, A. J. Head and R. J. Williams, *J. Chem. Soc.* 453 (1952); *Ibid.* 1715 (1953).
[17] F. Daniels and P. L. Veltman, *J. Chem. Phys.* **7**, 756 (1939).

reaction should apply, and again the product (tigogenin) is the stable isomer at C-22. Evidently the reaction conditions furnish sufficient activation to permit the approach of the alcohol from the more hindered side. Accordingly, we assign to the ketals and the hemiketal the stable structures indicated in formulas (II) to (V) and presume that their epimers are rather short lived under the conditions of our reactions.* These considerations provide an additional argument[5] against the suggestion[18] that *cyclo*pseudotigogenin is the 22-epimer of (VIb) because the cyclization product of (VIIb) contained no detectable amounts of *cyclo*pseudotigogenin, although *cyclo*pseudosapogenins do not isomerize to sapogenins under the conditions of the reaction.[2]

Our observations demonstrate that C-22 ketals can undergo bond ruptures and bond formations at C-22 under neutral conditions. No similar exchange reactions with aliphatic alcohols have been described for the known bicyclic ketals and none are to be expected, since the cyclization of pseudotigogenin and of (VIIb) with the C-26 carbinol group proceed in the presence of a large excess of a competing external alcohol. This different behavior could be caused by the lesser thermodynamic stability or by the greater flexibility of the monocyclic compounds. If stability is the important factor, exchange reactions analogous to those found with the less stable monocyclic ketals might also occur with the unstable C-22 epimers of the known *spiro* ketals and result in a change of their configuration at C-22. In that case it may not be sufficient merely to avoid acid conditions if the configuration at C-22 is to be preserved in a reaction that alters the relative stabilities of C-22 epimers. In view of this it does not seem superfluous to point out that our data are consistent with the assignment of Callow for the natural sapogenins and are not in conflict with the seemingly opposing assignment made by Wall for the *cyclo*pseudosapogenins.

Equilibration of the *iso* and normal sapogenins shows an equilibrium constant of 1/3 to 1/4 which at 350°K corresponds to ΔF of 760 to 960 cal.[19,6] The free-energy difference (A) caused by an exchange of an axial for an equatorial methyl at C-25 can now be estimated as about 900 cal.† On the other hand, if the normal and *iso*-sapogenins both possess an equatorial methyl at C-25 and differ in their configuration at C-22, their stability difference (B) should approximate that between ketal (III) and its epimer. If the difference were no larger than about 1000 cal, the detection of this epimer of (III) or (IV) should have been possible by spectrographic means after exposure to acid and alcohol inasmuch as the ketal group gives rise to strong bands, which can hardly be assumed to be invariant to a change of configuration. We

* The alternative possibility that the transition states are more nearly tetrahedral than trigonal and therefore favor the more stable configurations at C-22, would also account for our observations.

† Estimate based on a ΔF of about 1800 cal between equatorial and axial methyl*cyclo*hexane.[20] Our earlier[1] estimate of 800 + r cal included a term (r) for the skewed interaction between the pyranoid oxygen and the C-27 methyl. In the light of the recent discussion of Dauben and Pitzer [20] this term should be small or negligible, since a staggered methyl does not lead to the same non-bonded interactions as are present in axial *cyclo*hexanol. On the other hand, the sum of the two skewed interactions between an axial furanoid oxygen and C-24 and C-26 cannot be neglected but should aproximate 800 to 900 cal[20,21] On the basis of these values the difference between the two conformations (XVb) and (XVIb) that were shown in our older analysis[1] reduces to the interaction of C-21 with the axial H at C-26 in (XVIb). Judging from the rapid increase in ΔF with increasing bulk of an axial alkyl group,[20] this term (s) must be large and hence (XVIb) appreciably less stable than (XVb). It seems justified, therefore, to eliminate (XVIb) from this discussion.

[18] R. K. Callow and V. H. T. James, *Chem. & Ind.* 691 (1954).
[19] M. E. Wall, S. Serota and L. P. Witnauer, *J. Amer. Chem. Soc.* **77**, 3086 (1955).
[20] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* **77**, 5562 (1955).
[21] S. J. Angyal and D. J. McHugh, *Chem. & Ind.* 1147 (1956).

conclude therefore that only (*A*) agrees with the experimentally determined value for sapogenin equilibration, while (*B*) is larger than this. If the angle between corresponding bonds were the same in the sapogenins and *cyclo*pseudosapogenins, this conclusion should apply to both. However, normal bond angles cannot prevail if the configuration at C-20 is inverted, because this would lead to a prohibitively short distance[15] between C-18 and C-21. This strain should result in a displacement of C-21 towards the plane of ring *E* in such a way that the angular deflections are held to a minimum.[3c] This distortion lengthens the distance of C-21 from the proximal substituent at C-22 in ring *F* and thereby diminishes the difference (*B*). Consequently our findings cannot be applied to the *cyclo*pseudosapogenins. We cannot estimate the magnitude of this effect, but, if the distortion of the molecule reduces (*B*) to a value less than (*A*), the assignments of Wall and of Callow would be reconciled.

The key step used in demonstrating identical configurations at C-22 for *cyclo*pseudotigogenin and tigogenin consisted in a hydrogenation of a $\Delta^{20(21)}$-unsaturated sapogenin with platinum in non-specified neutral solvents.[5] Since nickel evidently can substitute an ethoxy for a hydroxy group* at C-22 as indicated by the conversion of (I) to (III), we have tested the stability of compound (III) to the action of platinum in methanol. At least with the amounts of catalyst used no appreciable exchange was observed.

The formation of the *exo*cyclic vinyl ether (VIIa) is in contrast to the eliminations described for the reduction product of Kaufmann and Rosenkranz[7] and for the sapogenins which always yielded the $\Delta^{20(22)}$-isomer.† The reason for this difference probably lies in the milder reaction conditions used by us. In fact, the more facile abstraction of a proton from C-23 rather than from C-20, which characterized our eliminations in the presence of acetic acid, may have its counterpart in certain acid-catalyzed reactions of the sapogenins such as bromination[22] and deuterium exchange.[23‡] If preferential protonation occurs on that oxygen which is not part of the furanoid ring, just as it must be in the acid-catalyzed desaturation of compound (III), the hydrogen most easily substituted at C-23 can be expected to be the equatorial one, since this bond would be coplanar with and antiparallel to the strongest electron-withdrawing group. Other workers[22,24] have suggested the axial conformation for the primary bromination product in analogy to observations with *cyclo*hexanones. Spectrographic observations[25] indicate, however, that the predominant[22] monobromide of tigogenin possesses an equatorial bromine.

* In this case we prefer this explanation to the one given for the alkylation of amines by alcohols in the presence of nickel, as the latter process requires conditions which permit the dehydrogenation of the alcohol to the aldehyde (either no added hydrogen or high temperatures). L. T. Plante, W. G. Lloyd, C. E. Schilling and L. B. Clapp, *J. Org. Chem.* **21**, 82 (1956); L. T. Plante and L. B. Clapp, *J. Org. Chem.* **21**, 86 (1956).

† The presence of the Δ^{22}-isomer as a contaminant of some preparations of pseudosapogenin diacetates has been suspected by A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.* 2807 (1955). Our results do not verify their predictions as to the optical rotation of the *exo*cyclic product. Its possible role as an intermediate in other reactions of the sapogenins has been discussed by D. H. Gould, H. Staeudle and E. B. Hershberg, *J. Amer. Chem. Soc.* **74**, 3685 (1952).

‡ Admittedly the site of these reactions has not been proven beyond doubt, but since two hydrogens can be replaced by either deuterium or bromine at least one should come from C-23. Reaction at C-23 has been assumed in virtually all discussions of this topic.

[22] M. E. Wall and H. W. Jones, *J. Amer. Chem. Soc.* **79**, 3222 (1957); and references cited in this paper.
[23] R. K. Callow, V. H. T. James and P. N. Massy-Beresford, *Chem. & Ind.* (*Rev.*) 26 (1956).
[24] D. A. H. Taylor, *Chem. & Ind.* 1066 (1954).
[25] D. H. R. Barton, J. E. Page and C. W. Shoppee, *J. Chem. Soc.* 331 (1956).

EXPERIMENTAL*†

3β, 26-Diacetoxy-25a-cholestane-16,22-dione (5,6-dihydrokryptogenin diacetate) (I). A solution of 677 mg of kryptogenin diacetate in 127 ml of 95% ethanol was stirred magnetically with 1·5 g of pre-reduced 1% palladium–calcium carbonate[1] in an atmosphere of hydrogen. The product was freed of catalyst by passage through a short column of silica gel–Celite and recrystallized from methanol and from ligroin to give 541 mg of compound (I), m.p. 121–123·5°. The spectrum retained the carbonyl peaks (5·77 and 5·82 μ) of the starting compound, but lost those at 12·28 and 12·45 μ (Δ^5).[26] A m.p. of 121–123° has been reported for (I) obtained with different catalysts.[27]

22a-Ethoxy-5α, 25a-furostan-3β, 26-diol diacetate (III). A solution of 261 mg of 5,6-dihydrokryptogenin diacetate (I) in 20 ml of absolute ethanol and a suspension of 2·3 g of freshly prepared Raney nickel[28]‡ in 3 ml of the same solvent were shaken in an atmosphere of hydrogen for 70 min. Gas uptake ceased after 35 min. The catalyst was removed by centrifugation and the product was recrystallized from 95% ethanol. Compound (III) had m.p. 154–157°. The yield was 160 mg. The analytical sample was dried at 80° and showed $[\alpha]_D$ −35° (*c*, 0·4 in ethanol). *Anal.* Calcd. for $C_{33}H_{54}O_6$: C, 72·48; H, 9·96. Found: C, 72·73; H, 10·22 per cent. The ratio of (III) to (II) as determined by the infrared spectrum of the crude reduction product was very much lower, when 138 mg of (I) in 95% ethanol were shaken with 238 mg of nickel and only 48 mg of (III) were obtained.

A solution of 2·5 mg of compound (III) in 1·5 ml of methanol was heated under reflux for 1 hr. The dried residue showed the infrared spectrum of (III). Chromatography of (III) on magnesium silicate–Celite led to a complex mixture, which showed the vinyl ether band.

5α,25a-Furostan-3β,22a,26-triol 3,26-diacetate (II). A solution of 50 mg of compound (III) in 3·75 ml of 80% acetic acid was kept at 25° for 2 hr and then equilibrated rapidly between alcohol-free ether and more than 2 equivalents of aqueous sodium carbonate. The ether phase was washed with more carbonate and repeatedly with water and was evaporated to dryness. The residue on recrystallization from light petroleum gave 43 mg of hemiketal (II). M.p.s of 112–114·5° and of 99–102° were observed for two different preparations, which possessed identical infrared spectra (λ_{max} 2·79, 5·77 μ, and those in Table I). $[\alpha]_D^{23}$ −23° (*c*, 0·5 in 95% ethanol). *Anal.* Calcd. for $C_{31}H_{50}O_6$: C, 71·77; H, 9·72. Found C, 71·87; H, 10·00 per cent.

* All melting points reported are corrected. Unless when noted otherwise, compounds were dried at room temperature for analysis and physical measurements, and infrared spectra were measured in carbon disulfide in 1 per cent solutions. Compound (VIb), which is less soluble, was examined also as a pressing in potassium bromide. The silica gel (Davison)–Celite (2:1) used in chromatography was pre-washed (K. N. Trueblood and E. W. Malmberg, *J. Amer. Chem. Soc.* **72**, 4112 (1950)). The unwashed product when suspended in water lowered its pH from 5·9 to 5·4, while Drierite raised it to 7·1. The ligroin used had boiling range of 90–96°, and the light petroleum 60–70°. The ether extracts of the reaction products were evaporated at room temperature under a current of nitrogen. No sodium sulfate or other chemical drying agent was employed.

† The stereonomenclature used follows the proposal of C. Djerassi, T. T. Grossnickle and L. B. High, *J. Amer. Chem. Soc.* **78**, 3166 (1956). Specifically, the terms "22a" and "25a" denote configurations identical with those in tigogenin.

‡ The W-5 catalyst used was prepared on 0·1 scale and washed with 5 l. of water. Excessive washing and too rapid stirring gave an inactive product.

[26] H. Hirschmann, *J. Amer. Chem. Soc.* **74**, 5357 (1952).

[27] R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *J. Amer. Chem. Soc.* **69**, 2199 (1947); A. L. Nussbaum, A. Sandoval, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.* **17**, 426 (1952).

[28] H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.* **70**, 695 (1948).

A sample heated under reflux in 95% ethanol for 70 min showed no change in spectrum.

22a-Methoxy-5α,25a-furostan-3β,26-diol diacetate (IV). A solution of 11 mg of ketal (III) in 0·8 ml of dry methanol and 0·2 ml of glacial acetic acid was kept at room temperature for 200 min and worked up as described for (II). Recrystallization from methanol gave the methyl ketal (IV), m.p. 112·5–117°. The bands at 9·08 and 9·38 μ serve best for the differentiation of this compound. *Anal.* Calcd. for $C_{32}H_{52}O_6$: C, 72·14; H, 9·84. Found: C, 71·71; H, 10·10 per cent.

5α,25a-Δ²²-Furosten-3β,26-diol diacetate (VIIa). A solution of 21·3 mg of the hemiketal (II) in 1 ml of benzene was shaken with 400 mg of Drierite at room temperature for 8 hr in the dark. Compound (VIIa) (18·7 mg) was obtained by centrifuging and four washings with benzene. (Losses due to adsorption occurred consistently. To prevent this a trial run was treated with methanol just before centrifuging. The product contained about 45 per cent of (IV).) Olefin (VIIa) showed λ_{max} at 5·77, 5·91 μ and those given in Table 1. Material with the same absorption characteristics was obtained from (III) adsorbed on 55 parts of silica gel–Celite in a fraction eluted with benzene containing 5 per cent of ether. Complete conversion of 31 mg of (III) to (VIIa) by shaking with Drierite required three treatments (550, 520 and 1280 mg of calcium sulfate) to yield (VIIa), with $[\alpha]_D^{23} + 3°$ (*c*, 0·6 in 95% ethanol).

Product (VIIa) contaminated with (II) resulted when 3 mg of (III) were kept in 1·2 ml of dry benzene and 0·25 ml of dry acetic acid for 200 min at room temperature and worked up as described for (II). A sample of the olefin (VIIa) stored for 5 weeks lost its absorption band at 5·91 μ and showed new absorption in the hydroxyl and ketone region. All experiments recorded for (VIIa) were done on freshly prepared samples that had been checked spectrographically.

3β-Acetoxy-16β-hydroxybisnorcholanic 22→16-lactone (IX). A mixture of 16 mg of olefin (VIIa), 16 mg of chromium trioxide and 3·8 ml of 99·5% acetic acid was kept at 25° for 270 min. Excess of oxidant was reduced with methanol and the product was extracted with ether. The neutral fraction (13 mg) clearly showed the peak of the normal lactone at 8·51 μ, but not that of its 20-epimer at 8·61 μ.[15] It was hydrolyzed with potassium hydroxide and *tert.*-butanol[29] for 3 hr at room temperature and again separated into neutral (3·4 mg with λ_{max} 240 mμ and extinction equivalent[29] to 1·2 mg of 3β-hydroxy-Δ¹⁶-*allo*pregnen-20-one*) and acidic compounds. The latter were relactonized with hydrochloric acid and the product (6·8 mg) was acetylated with acetic anhydride and pyridine at room temperature. The acetate had the infrared spectrum of 3β-acetoxy-16β-hydroxybisnor*allo*cholanic 22→16-lactone and upon recrystallization from 95% ethanol and from methanol showed m.p. 217–220°, undepressed by admixture of a reference sample.[15]

22a-Ethoxy-5α,25a-furostan-3β,26-diol (V). A mixture of 30 mg of ethyl ketal (III), 9 ml of methanol and 0·6 ml of 5% aqueous potassium carbonate was warmed gently to effect solution and kept at room temperature for 24 hr. The mixture was concentrated to about 2 ml under a current of nitrogen and distributed between ether and water. The ether phase yielded 24 mg of residue, which was recrystallized from ethanol and from acetone. The compound melted with evolution of gas at about

* The most likely explanation for the formation of this product is a shift of the double bond by chromic acid analogous to the one observed with phosphoric acid.

[29] M. E. Wall, H. E. Kenney and E. S. Rothman, *J. Amer. Chem. Soc.* 77, 5665 (1955).

200–205°. *Anal.* Calcd. for $C_{29}H_{50}O_4$: C, 75·28; H, 10·89. Found: C, 75·22; H, 11·14 per cent. This sample was dried at room temperature; another which was dried at 80° lost about 3 per cent of its weight and gave C, 75·93; H, 10·65 per cent, suggesting that partial elimination of ethanol had occurred.

5α,25a-Δ²²-Furosten-3β,26-diol (VIIb). Olefin (VIIa) (18·5 mg in 4·5 ml of methanol) was hydrolyzed with 0·4 ml of 5% potassium carbonate under nitrogen for 24 hr. The product (15·5 mg) was isolated by ether extraction and recrystallized from acetone. Fine needles were obtained, which showed partial or complete fusion near 152°, followed by resolidification on further heating. The final m.p. (209°) suggests conversion to tigogenin during heating. Only the sample used for combustion was dried at 100°. *Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77·83; H, 10·65. Found: C, 77·40; H, 10·87 per cent. The principal peaks include λ_{max}^{KBr} 5·91, 7·64, 7·73, 8·19, 8·59, 8·83, 9·25, ~9·59, 10·18, 10·40 and 10·62 μ. This product, which was handled in glassware pre-washed with carbonate and with water, was free of tigogenin in spectrographically detectable amounts. When these precautions were not taken, recrystallization from alcoholic solvents led to a mixture of (VIIb) and (VIb).

Other conversions catalyzed by acetic acid. In general reactions were performed on 2·5 mg samples of starting compound, which were dissolved in four volumes of the alcohol listed (usually 0·4 ml) and one volume of glacial acetic acid and maintained at room temperature. Reaction times in min are given in parentheses. Products were isolated as described for (II) and examined spectrographically without purification. In every case the curve of the crude product was in very close agreement with that obtained with our best reference specimen. Reaction (*a*) (III) + methanol (200) → (IV); (*b*) (III) + methanol (10) → (IV); (*c*) (IV) + ethanol (200) → (III); (*d*) (VIIa) + methanol (10) → (IV); (*e*) (VIIa) + ethanol (180) → (III); (*f*) (II) + ethanol (10) → (III); (*g*) (VIII) + ethanol (200) → (VIII); (*h*) (III) + ethanol (200) → (III). [The product of (*h*) was chromatographed on paper in the system *iso*octane, methanol and water (20 : 17 : 3 by volume) and treated with trichloroacetic acid in 95% ethanol.[30] As with pure (III), only a single spot was seen (R_F 0·84). A larger run (15·2 mg) of reaction (*h*) was recrystallized once from 95% ethanol. The crystals melted at 153–156°, the mother liquor (1·8 mg) showed signs of some decomposition, but consisted mainly of ketal (III).] (*i*) (V) (9·8 mg) + ethanol (2·6 ml) (135) → (VIb) [identity confirmed by m.p. (205–209°) and mixture m.p. and by m.p. (203–209°), mixture m.p. and infrared spectrum of acetate]; (*j*) (VIIb) + ethanol (10) → (VIb) [the purity of the crude reaction product was confirmed by infrared spectroscopy after acetylation, the identity also by the m.p. and mixture m.p. (both 209°) of the recrystallized acetate]; (*k*) when 2·3 mg of (III), 2 ml of ethanol and 0·5 ml of acetic acid were heated under a reflux, the product showed only maxima attributable to either (III) or (VIII). (III) predominated after 2, (VIII) after 8½ hr.

Pyrolyses. All reactions were run in small glass tubes, which were evacuated and sealed. The tubes were inserted into a pre-heated microbomb oven and removed from it hot at the end of the reaction time. The opened tubes were dried to remove ethanol and their contents were examined spectrographically. Differentiation of (VIIa) and (VIII) was facilitated by the fact that (VIIa) has extinction minima at 8·44 and 7·69 μ and (VIII) at 8·56 μ, which nearly coincide with maxima of the other

[30] C. de Courcy, *J. Endocrinol.* **14**, 164 (1956). This procedure is a modification of one introduced by E. Heftmann and A. L. Hayden, *J. Biol. Chem.* **197**, 47 (1952).

olefin. Compound (III) was estimated by the apparent extinction at 9·41 μ. In the conditions specified below the first figure refers to the reaction temperature, the second to the time in minutes:

(i) *Clean glass tubes.* About 2·5 mg of (III) (*a*) 195°, 180; (*b*) 186°, 20; (*c*) 170°, 15; (*d*) 157°, 20; (*e*) 158°, 30. The ratio of (VIIa) to (VIII) varied irregularly as it increased in the sequence (*c*), (*a*), (*e*), (*d*), (*b*), the content of (III) from (*a*) to (*e*) was about 0, 13, 15, 22, 20 per cent, respectively. (*f*) (VIII) 158°, 280 showed no change; (*g*) product of (*a*) 195°, 240 was almost completely converted to (VIII); (*h*) product of (*e*) + 1 ml of methanol 158°, 30 → mixture of (IV), (VIIa) and (VIII).

(ii) *Tubes coated with carbonaceous residue.* These were obtained by keeping tubes which had been evacuated and then filled with ethylene at 450° for 17 hr. Pyrolyses of either (III) or (VIIa) for 30 min at 158° gave (VIII) runs *i*, *j*.

(iii) *Silvered tubes.* These were pre-treated with Tollen's reagent and lactose, and then thoroughly washed and dried: (*k*) (III) 158°, 30 → (VIIa) and (III) (ca. 28%); (l) (III) 158°, 90 → (VIIa) and (III) (ca. 34 per cent); product of (*k*) + 0·2 ml of methanol 158°, 30 → (IV) and (VIIa); product of (l) + 0·25 ml of ethanol 158°, 30 → (VIIa) and (III) (ca. 40 per cent).

Other reactions of 5α,25*a*-Δ^{22}-*furosten*-3β,26-*diol diacetate* (VIIa). A solution of 2·7 mg of (VIIa) in 2 ml of methanol was shaken with 320 mg of Drierite for 8 hr. About 55 per cent was converted to (IV).

A solution of 3·5 mg of (VIIa) in 6 ml of dry dioxan was stirred magnetically with 18 mg of platinum (which had been pre-reduced and washed with dry dioxan) in an atmosphere of hydrogen for 135 min. No change in spectrum was observed.

When this material was treated with 0·9 ml of acetic acid and 0·1 ml of concentrated hydrochloric acid at 23° for 15 hr, the product no longer showed absorption at 5·91 μ. There was new carbonyl absorption near 5·83 μ, but no hydroxyl peak. The Beilstein test was positive.

A solution of 2·3 mg of (VIIa) in 0·95 ml of acetic and 0·05 ml of 85% phosphoric acids was kept at room temperature for 200 min. The product isolated as described for (II) gave an infrared spectrum characteristic of (VIII).

Treatment of ketal (III) *with platinum.* Compound (III) (3·2 mg), 25 mg of Adam's platinum dioxide catalyst and 6 ml of methanol were shaken with hydrogen for 90 min. The product was no longer completely soluble in carbon disulfide, evidently owing to partial deacetylation. The spectrum was essentially that of ketal (III), but showed a weak shoulder at 9·08 μ (cf. Table 1, compound (IV)) which was not seen in a control without platinum.

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MACROLIDE ANTIBIOTICS—VII*

THE STRUCTURE OF NEOMETHYMYCIN†

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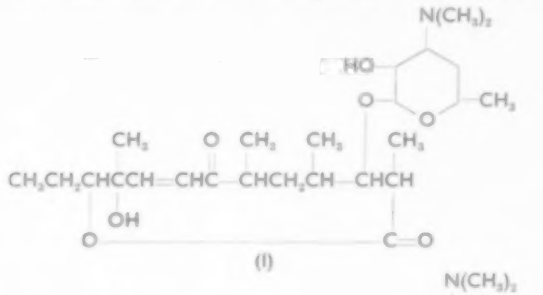
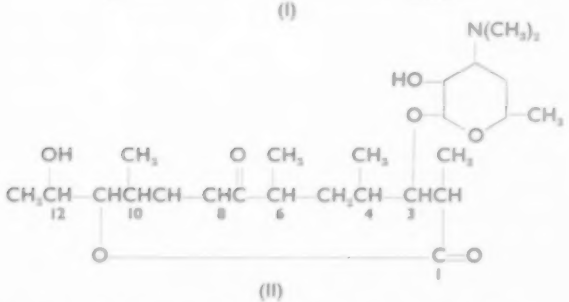
Abstract—Degradation experiments are described which establish rigorously structure (II) for neomethymycin ($C_{23}H_{43}NO_7$). This antibiotic belongs, therefore, to the macrolide group and differs from methymycin (I) only in the location of one hydroxyl group, which results in marked changes in chemical behavior. The two antibiotics appear to have the same absolute configuration at the relevant asymmetric centers as inferred by the isolation of a common degradation product and the general similarity of certain rotatory dispersion curves. The position of the hydroxyl group at C-12 in neomethymycin is noteworthy from a biogenetic standpoint.

THE term "macrolide"[1] encompasses a group of therapeutically and biogenetically important antibiotics characterized by a lactone moiety of medium or large ring size. Methymycin[2] was the first antibiotic of this class for which a complete structure (I) could be presented[3–6] and from its mother liquors§ there has now been obtained



(I)



(II)

* Paper VI, C. Djerassi and O. Halpern, *J. Amer. Chem. Soc.* **79**, 3926 (1957).

† For preliminary communication see C. Djerassi and O. Halpern, *J. Amer. Chem. Soc.* **79**, 2022 (1957)

‡ Postdoctorate research fellow, 1956–1957.

§ Kindly supplied by Dr. J. Vandeputte (Squibb Institute for Medical Research, New Brunswick, New Jersey), who first encountered the chloroform solvate of a second antibiotic in these mother liquors.

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[2] M. N. Donin, J. Pagano, J. D. Dutcher and C. M. McKee, *Antibiotics Annual* 1953–1954 p. 179. Medical Encyclopedia Inc., New York.

[3] C. Djerassi, A. Bowers and H. N. Khastgir, *J. Amer. Chem. Soc.* **78**, 1729 (1956).

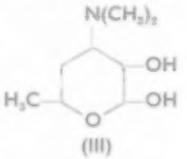
[4] C. Djerassi, A. Bowers, R. Hodges and B. Riniker, *J. Amer. Chem. Soc.* **78**, 1733 (1956).

[5] C. Djerassi and J. A. Zderic, *J. Amer. Chem. Soc.* **78**, 2907 (1956).

[6] C. Djerassi and J. A. Zderic, *J. Amer. Chem. Soc.* **78**, 6390 (1956).

another antibiotic for which we propose the name "neomethymycin" because of its close structural and stereochemical relationship to methymycin (I). On the basis of degradation experiments described in detail in this paper, neomethymycin is assigned formula (II).

Neomethymycin was first isolated in pure form by chromatographic separation from methymycin (I), since it proved to be slightly more polar. Subsequently, it was found that the bulk of the material could be separated quite readily as the methylene dichloride solvate and analysis showed it to be isomeric ($C_{25}H_{43}NO_7$) with methymycin (I)[2] and pikromycin.[7] Functional group analysis indicated the presence of at least six C-methyl and two N-methyl groups and the close similarity of the ultraviolet (λ_{max}^{EtOH} 227·5 mμ, log ε 4·10) and infrared [$\lambda_{max}^{CHCl_3}$ 2·93 μ (hydroxyl), 5·76 μ (lactone), 5·90 μ (unsaturated ketone) and 6·10 μ (double bond)] spectra suggested that the same chromophores were present in methymycin (I) and neomethymycin. Hydrolysis with hydrochloric acid[4] led in good yield (as the hydrochloride) to the amino-sugar desosamine (III),[8,9] which had already been isolated earlier from the antibiotics pikromycin,[7,9] erythromycin,[8] narbomycin[10] and methymycin.[4] Consequently, the difference between methymycin (I) and neomethymycin had to reside in the aglycone portion of the molecule and main attention, therefore, was paid to the isolation of this aglycone, named "neomethynolide", and to the determination of its structure.



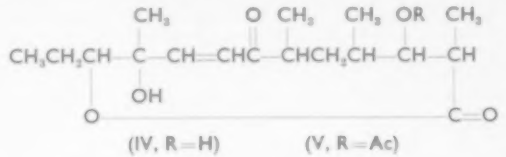
(III)

Careful hydrolysis of neomethymycin with sulfuric acid, under conditions[6] that in the case of methymycin (I) led to methynolide (IV), furnished the desired crystalline neomethynolide accompanied by an isomer, *cyclo*neomethynolide, which formed an integral part of the structure proof. Both substances possessed the same empirical formula ($C_{17}H_{28}O_5$) as methynolide (IV)[5,6] and spectral examination showed that neomethynolide rather than *cyclo*neomethynolide (*vide infra*) represented the true aglycone of neomethymycin (II). Thus it exhibited the same ultraviolet and infrared maxima (in the 2–6·2 μ region) as the parent antibiotic, and neither it nor neomethymycin were oxidized by periodic acid. In marked contrast to methynolide (IV), which forms only a monoacetate (V), neomethynolide upon acetylation led to a diacetate, indicating the absence of a tertiary hydroxyl group.

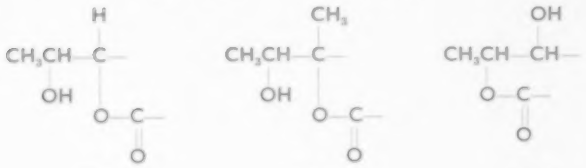
While neomethynolide—just like methynolide (IV)—was resistant to periodic acid, lithium aluminum hydride reduction followed by treatment with periodic acid resulted in the consumption of one equivalent of reagent and the formation of acetaldehyde. It should be noted that similar treatment of methynolide (IV)[5,6] or tetrahydrokromycin (XXVIII)[11] (a transformation product of pikromycin[7]) yielded propionaldehyde rather then acetaldehyde, thus defining one major point of structural difference

[7] H. Brockmann and W. Henkel, *Chem. Ber.* **84**, 284 (1951).
[8] R. K. Clarke, *Antibiot. & Chemother.* **3**, 663 (1953); E. H. Flynn, M. V. Sigal, P. F. Wiley and K. Gerzon, *J. Amer. Chem. Soc.* **76**, 3121 (1954).
[9] H. Brockmann, H. B. König and R. Oster, *Chem. Ber.* **87**, 856 (1954).
[10] R. Corbaz, L. Ettlinger, E. Gaumann, W. Keller, P. Kradolfer, E. Kyburz, L. Neipp, V. Prelog, R. Reusser and H. Zahner, *Helv. Chim. Acta* **38**, 935 (1955).
[11] R. Anliker and K. Gubler, *Helv. Chim. Acta* **40**, 119 (1957).

between neomethymycin and these other macrolide antibiotics. The resistance of neomethynolide towards periodic acid, the lability of its lithium aluminum hydride reduction product when exposed to the same reagent and the isolation of acetaldehyde are only compatible with partial structures (VI), (VII) or (VIII), which were supported by the positive iodoform test exhibited by neomethynolide.*

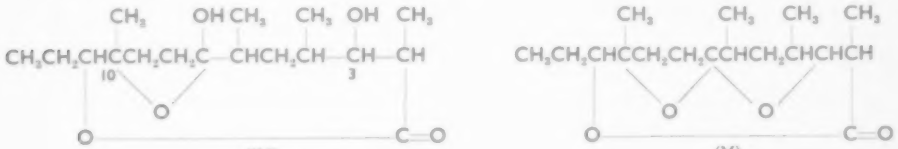


(IV, R = H) (V, R = Ac)



(VI) (VII) (VIII)

Hydrogenation of neomethynolide with palladized charcoal led to dihydroneomethynolide [subsequently shown to be (XXVI)] in which the double bond of the $\alpha\beta$-unsaturated ketone grouping had been reduced. This was demonstrated readily by the disappearance of the high-intensity ultraviolet absorption band of neomethynolide at 227·5 mμ as well as of the infrared bands at 5·90 and 6·10 μ associated with that chromophore. The corresponding derivative in the methymycin (I) series, dihydromethynolide[6] [(IV) with double bond reduced] appears to exist almost exclusively in the hemiketal form (IX)†, since it exhibits[6] a plain rotatory dispersion curve‡ and only a single infrared carbonyl band associated with the lactone group. Further, dihydromethynolide was found[6] to be extremely sensitive to acid, which transformed it almost instantaneously to the *spiro*ketal (X).



(IX) (X)

With these observations in the methymycin (I) series in mind, it should be noted that dihydroneomethynolide (XXVI) shows (Fig. 2) an anomalous rotatory dispersion curve, which can only be attributed[12] to a keto group, exhibits two infrared carbonyl

* Since the $\alpha\beta$-unsaturated ketone system of methymycin (I)—which in this paper has also been shown to be present in neomethymycin (II)—is capable of undergoing a reverse aldol condensation in an alkaline medium[4,5,6] with generation of a methyl ketone, which could then exhibit a positive iodoform reaction, it was necessary to exclude this possibility. This was done by examining dihydroneomethynolide (XXVI) which still yielded iodoform when treated with hypoiodite.

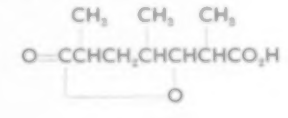
† The reason that the hydroxyl group at C-10 rather than at C-3 is assumed to be involved in hemiketal formation is due to the observation that dihydromethymycin [(I) with double bond reduced] also exhibits a plain rotatory dispersion curve[6] and in this substance only the C-10 hydroxyl group is available for cyclization to a hemiketal [(IX) with desosamine attached at C-3].

‡ For nomenclature in rotatory dispersion work see C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957).

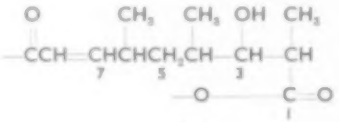
[12] See C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957).

bands [$\lambda_{max}^{CHCl_3}$ 5·77 μ (lactone) and 5·85 μ (saturated ketone)] and most importantly is completely stable to acid. It is obvious, therefore, that the secondary hydroxyl group of neomethymycin, which gives rise to acetaldehyde, is not situated favorably with respect to the carbonyl center for hemiketal formation (in contrast to the tertiary hydroxyl group at C-10 of methymycin) and that this has to be attributed either to conformational or structural differences. If we assume that the rest of the molecule (C-1 to C-10) of methynolide (IV) and neomethynolide [subsequently shown to be (XIX)] is identical, then partial structure (VIII) could tentatively be excluded, since it should be able to participate in hemiketal or *spiro*ketal formation. The second alternative (VII) could be eliminated quite definitely because the nonvolatile residue from the lithium aluminum hydride–periodic acid reaction sequence on dihydroneomethynolide* did not give a positive iodoform test. If partial structure (VII) had been present, then a methyl ketone would have been formed which should have responded to hypoiodite as has in fact been observed in the pikromycin series.[11] From the above evidence, the partial formulation (VI) can be put forward provisionally for one terminal of the neomethymycin molecule and decisive support for it will be discussed below in connection with *cyclo*neomethynolide.

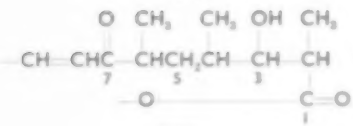
The analytical and spectral results suggested a close similarity between methynolide (IV) and neomethynolide and this supposition was strengthened greatly when neomethynolide was subject to ozonolysis,† whereupon the lactonic acid (XI) was isolated readily. This acid had been obtained earlier by permanganate oxidation of pikromycin,[12] narbomycin[12] and methymycin[5,6] and is known to arise from the first seven carbon atoms involved in the lactone ring. Its formation from neomethymycin implies that one of the partial structures (XII), (XIII), (XIV) or (XV) must be present in neomethymycin.



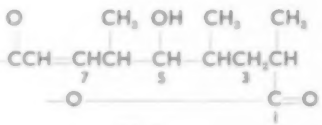
(XI)



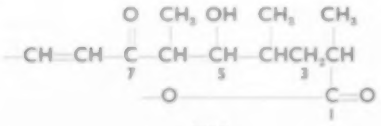
(XII)



(XIII)



(XIV)



(XV)

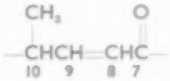
The lactonic acid (XI) and the partial structure (VI) are connected to each other, since they represent the two terminal points of the lactone ring; together they account

* The reaction was carried out with dihydroneomethynolide rather than neomethynolide in order to avoid any ambiguities arising from possible reverse aldolization.

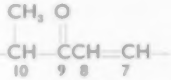
† This represents a marked improvement in yield over the earlier permanganate procedure[6,12] and consequently was also repeated with methynolide (IV), as reported in the experimental section.

[12] R. Anliker, D. Dvornik, K. Gubler, H. Heusser and V. Prelog, *Helv. Chim. Acta* **39**, 1785 (1956).

for thirteen of the seventeen carbon atoms of neomethynolide as well as for four of the five C-methyl groups. The position of the ultraviolet absorption maximum (227·5 mμ) of neomethymycin and neomethynolide precludes the location of the fifth C-methyl group on the double bond, from which it follows that the remaining four carbon atoms must be contained in unit (XVI) or (XVII).* In order to explain the ready formation of the lactonic acid (XI) by ozonolysis, one of the carboxyl groups of (XI) must have been formed by scission of the $\alpha\beta$-unsaturated ketone moiety, which, therefore, must be attached in one of the alternative manners indicated by expressions (XII)–(XV). It should be noted that the first two structures, (XII) and (XIII), bear the second hydroxyl group at C-3, which position has been established unequivocally as the site of substitution in methymycin (I).[5,6] The possibility that the hydroxyl group of neomethymycin is located at C-5 [(XIV) or (XV)]—a position preferred though not proved rigorously for pikromycin[11,14,15]—cannot be discarded with the evidence presented so far, although its stability under the acid cleavage conditions used for the preparation of neomethynolide would speak in favor of (XII) or (XIII).†



(XVI)



(XVII)

All these outstanding points could be settled by examining the second product of the acid cleavage of neomethymycin (II), which accompanied neomethynolide (XIX). This second substance, now named *cyclo*neomethynolide, was isomeric ($C_{17}H_{28}O_5$) with neomethynolide, but otherwise differed greatly from it. In contrast to neomethymycin (II) and neomethynolide (XIX), *cyclo*neomethynolide did not exhibit any ultraviolet absorption at 227·5 mμ and lacked the infrared bands at 5·90 and 6·10 μ typical of the unsaturated carbonyl system. The presence of a saturated ketone could be demonstrated by its anomalous rotatory dispersion with a negative single Cotton effect curve (Fig. 2) and the infrared band at 5·83 μ (in addition to the lactone band at 5·73 μ). The destruction of the unsaturated carbonyl chromophore was apparently caused by acid-catalyzed addition‡ of one of the hydroxyl groups, since acetylation of *cyclo*neomethynolide [subsequently shown to be (XXII)] yielded a mono-acetate, which did not exhibit any more hydroxyl absorption in the infrared region. Under the same conditions, neomethynolide (XIX) formed a diacetate (XX). Oxidation of *cyclo*neomethynolide with chromium trioxide–acetone reagent[16] afforded in excellent yield dehydro*cyclo*neomethynolide (XXIV) in which the free hydroxyl group had been converted into a ketone function. Alkaline hydrolysis of dehydro*cyclo*neomethynolide (XXIV) followed by basification furnished 63 per cent of carbon dioxide, which meant that the new carbonyl group, and hence the hydroxyl group from which it was derived, had to be located β to the lactone carboxyl function. These results

* As indicated by the numbering system, unit (XVI) can only be combined with (XIII) or (XV), while (XVII) can only be combined with (XII) or (XIV).

† It was appreciated, however, that steric factors in the medium-sized lactone ring might in certain circumstances place such an argument on tenuous grounds.

‡ The acid-catalyzed addition of methanol to the double bond of methymycin (I) has already been described earlier.[6]

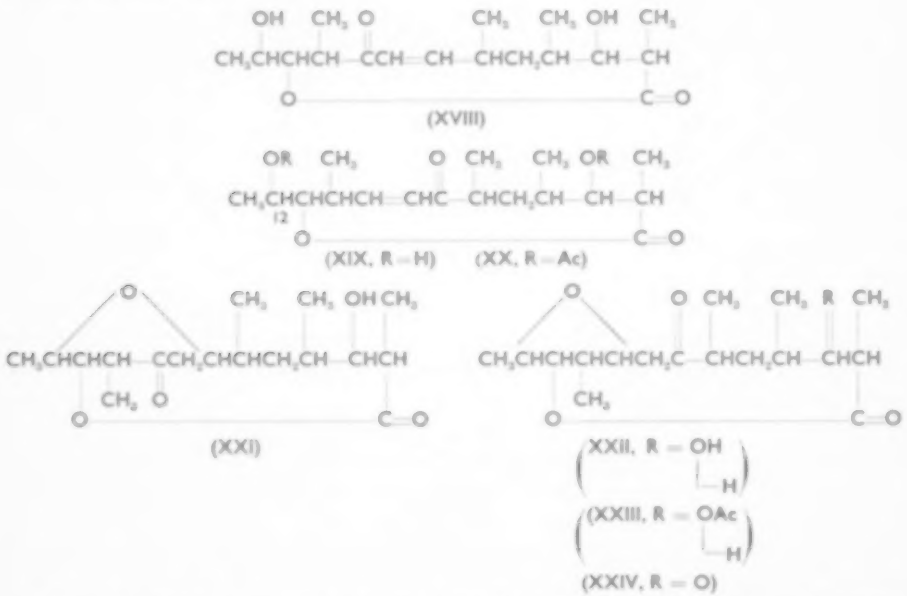
[14] H. Brockmann and R. Oster, *Chem. Ber.* **90**, 605 (1957).

[15] R. Anliker and K. Gubler, *Helv. Chim. Acta* **40**, 1768 (1957).

[16] See K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

rule out partial structures (XIV) and (XV) and prove that one of the hydroxyl groups of neomethymycin (II) and its transformation products must be located at C-3 rather than at C-5.

With the elimination of (XIV) and (XV), there remain only two possible structures [(XVIII) or (XIX)] for neomethynolide that can be constructed by combination of (VI), (XVI) or (XVII) and (XII) or (XIII). In order to differentiate between these two structural alternatives [(XVIII) or (XIX)], it will be necessary to consider again the behavior of *cyclo*neomethynolide (XXII). The latter must contain a new oxide ring, produced by addition to the double bond of the hydroxyl group present in (VI) or (VIII). Tentative reasons for preferring (VI) have been outlined above and this has now been confirmed fully by the observation that *cyclo*neomethynolide (XXII) did not yield any iodoform upon treatment with hypoiodite. If the hydroxyl group of (VIII) had been involved in the ether linkage, then alkaline hypoiodite would have resulted in opening of the lactone ring and formation of iodoform. Further supporting evidence for the location of the ether linkage was adduced when it was observed that *cyclo*neomethynolide—in contrast to neomethynolide (XIX)—did not react with periodic acid after lithium aluminum hydride reduction. On the basis of structure (XVIII) for neomethynolide, *cyclo*neomethynolide would have to be (XXI), while if (XIX) were the correct structure, *cyclo*neomethynolide would have to be formulated as (XXII). Clearly the latter is preferable, since it involves a five- rather than seven-membered oxide ring.



Two additional arguments in favor of structure (XIX) for neomethynolide can be presented. Base treatment of (XVIII) should lead, at least in part, to a cross-conjugated dienone by β-elimination and such a dienone would not be expected to absorb much above 255 mμ.[17] On the other hand, β-elimination of (XIX) would afford a linearly

[17] E. A. Braude and J. A. Coles, *J. Chem. Soc.* 2012 (1950).

conjugated dienone with appreciably higher absorption and, while no pure product was isolated, spectrophotometric examination of an ethanolic solution of neomethynolide (XIX) containing some sodium ethoxide showed the loss of the 227·5 mμ peak and the concomitant appearance of a new absorption maximum at 280 mμ. This is precisely the region where a dienone acid of structure (XXV) would be expected to absorb.

Further, the rotatory dispersion curve (Fig. 1) of neomethymycin (II) shows a general similarity to that of methymycin (I)[6] and this would hardly be expected of a structure based on (XVIII) where the entire environment is changed around the

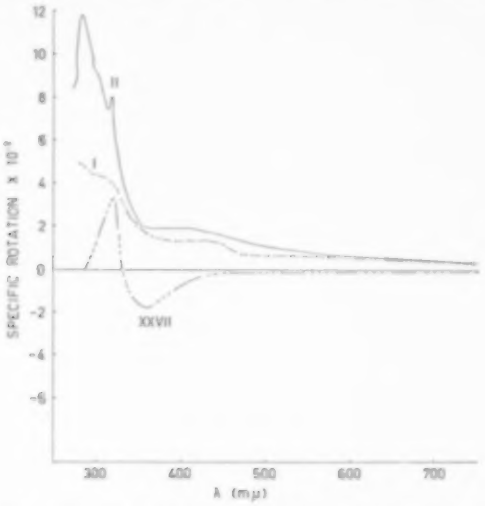


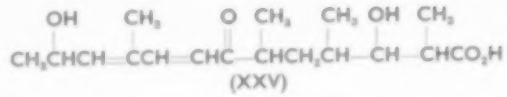
FIG. 1. Optical rotatory dispersion curves (dioxan solution) of methymycin (I), neomethy-mycin (II) and pikromycin (XXVII).

carbonyl chromophore, which would be chiefly responsible[12] for the characteristic rotatory dispersion features.

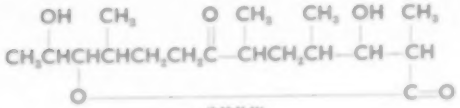
With the establishment of structure (XIX) for neomethynolide, there remains only the placement of the desosamine fragment (III) in order to arrive at a complete expression for the antibiotic itself. The glycosidic linkage could only involve the hydroxyl groups at either C-3 or C-12 and the general similarity of methymycin (I) and neomethymycin, carrying over even to their antibiotic activities,* would suggest that the sugar is attached at C-3 as has already been established[5,6] for methymycin (I). In fact, the lithium aluminum hydride–periodic acid sequence—described above for neomethynolide (XIX) and dihydroneomethynolide (XXVI)—was applied to neomethymycin itself and also yielded acetaldehyde. The conditions were such that it was rather unlikely that a glycosidic linkage could have been split but for further confirmation, neomethymycin was dissolved in warm sodium hydroxide solution and the resulting hydroxy acid was treated with sodium metaperiodate, which again produced acetaldehyde. The formation of acetaldehyde under these circumstances

* The microbiological assay, carried out at the Squibb Institute for Medical Research, indicated virtually identical activity for methymycin (I) and neomethymycin (II) except with *Bacillus subtilis* where the latter was effective at one-fourth the minimum inhibitory concentration of methymycin (I).

would only be possible if the hydroxyl group at C-12 were free, and neomethymycin can therefore be assigned structure (II).



(XXV)



(XXVI)

The general similarity of the rotatory dispersion curves (Fig. 1) of methymycin (I) and neomethymycin (II) coupled with the isolation of the same lactonic acid (XI)

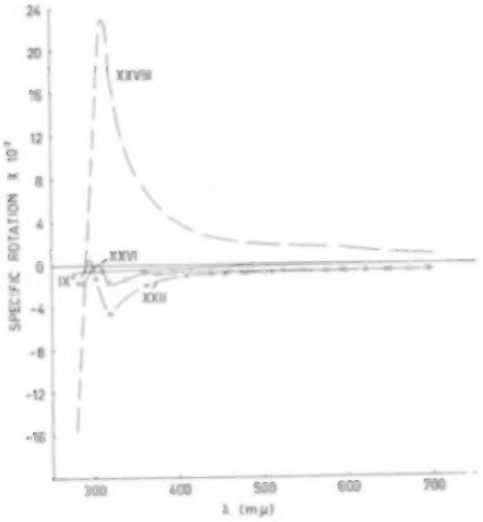
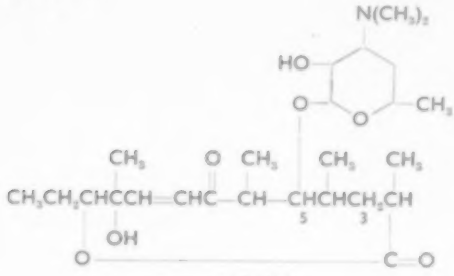


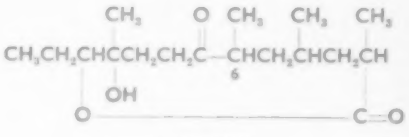
FIG. 2. Optical rotatory dispersion curves (dioxan solution) of dihydromethynolide (IX), *cyclo*neomethynolide (XXII), dihydroneomethynolide (XXVI) and tetrahydrokromycin (XXVIII).

from either antibiotic suggests that the two possess substantially the same conformation as well as identical absolute configurations at the relevant asymmetric centers. It is interesting to note that pikromycin,[7] which is isomeric with methymycin (I) and neomethymycin (II), exhibits a rotatory dispersion curve (Fig. 1) that is completely different yet yields the same lactonic acid (XI) upon oxidation.[13] On the basis of reported degradations[11,14,15] pikromycin can only have structures (XXVII) or (I) and, if the latter is correct, then pikromycin must be epimeric at C-3 with methymycin (I) and neomethymycin (II). Since this change alone is not likely to be responsible for the major rotatory dispersion difference between the antibiotics, which is further demonstrated by comparing the curves (Fig. 2) of dihydromethynolide (IX), dihydroneomethynolide (XXVI) and tetrahydrokromycin (XXVIII),[11] this implies that methymycin (I) and pikromycin must differ in absolute configuration at C-10 or C-11

or both, or that the conformation of the respective rings is different.* This latter possibility is not so far fetched, considering the subtle trans-annular factors that may control conformation in a medium-sized (twelve-)-membered lactone ring and in fact may even apply if pikromycin possesses structure (XXVII). If pikromycin differs from methymycin (I) only in the configuration at C-3, then it should be possible to interconvert these two antibiotics and attempts along those lines are currently in progress.



(XXVII)



(XXVIII)

The structure elucidation of antibiotics of this group is not only of intrinsic interest, but as the number of secure structure determinations among macrolide antibiotics increases—aside from methymycin (I) and neomethymycin (II) these include so far only magnamycin,[1] erythromycin[18] and most probably erythromycin B[19]—the statistical validity of biogenetic speculations[1,20] is strengthened. From that standpoint, neomethymycin (II) is important, since hydroxylation at C-12 represents an "extra" position in the sense discussed by Woodward.[1]

EXPERIMENTAL†

Isolation of neomethymycin (II). The first pure sample was secured by chromatographing the mother liquors from the original methymycin (I) isolation[2] on fifty times its weight of alumina, which was deactivated with 3 per cent of its weight of 10% aqueous acetic acid. The material was placed on the column in ether solution and eluted with ether containing 0·5 and then 1 per cent of methanol. Methymycin (I) appeared first followed by mixtures and gradually pure neomethymycin was obtained, which crystallized readily from ether–hexane, m.p. 156–158°, $[\alpha]_D$ +93°, λ_{max}^{EtOH} 227·5 mμ (log ε 4·10), $\lambda_{max}^{CHCl_3}$ 2·93, 5·76, 5·90 and 6·10 μ, rotary dispersion (Fig. 1) in dioxan (*c*, 0965) : $[\alpha]_{700}$ +58°, $[\alpha]_{589}$ +74°, $[\alpha]_{400\text{-}355}$ +202° (infl), $[\alpha]_{320}$ +809°, $[\alpha]_{317\cdot5}$ +736°, $[\alpha]_{285}$ +1190°, $[\alpha]_{275}$ +840°. *Anal.* Calcd. for $C_{25}H_{43}NO_7$: C, 63·94; H, 9·23; N, 2·98

* In contrast to dihydromethynolide (IX), tetrahydrokromycin (XXVIII) does not exist as a hemiketal (see rotatory dispersion (Fig. 2) as well as infrared spectrum[11] and this is undoubtedly due to conformational differences. In fact, the absolute configuration of C-6 in tetrahydrokromycin (XXVIII) may not be identical with that existing in pikromycin, since hydrogenation of a 5–6 double bond is involved in the production of (XXVIII).

† Melting points were determined on the Kofler block. Unless noted otherwise, all rotations were measured in chloroform solution. We are indebted to Mrs. Dolores Phillips for the infrared and ultraviolet spectra and to Mr. Joseph F. Alicino (Squibb Institute for Medical Research) for the microanalyses.

[18] P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, O. Weaver, U. C. Quarck, R. C. Chauvette and R. Monahan, *J. Amer. Chem. Soc.* **79**, 6062 (1957).

[19] P. F. Wiley, M. V. Sigal, O. Weaver, R. Monahan and K. Gerzon, *J. Amer. Chem. Soc.* **79**, 6070 (1957).

[20] A. J. Birch, *Progress in the Chemistry of Organic Natural Products* (Edited by L. Zechmeister) Vol. XIV, p. 202. Springer, Vienna (1957).

2 N-CH_3, 6·4; 6 C-CH_3, 19·2; mol. wt., 469·6. Found: C, 63·75; H, 9·04; N, 3·07; N-CH_3, 5·90; C-CH_3, 16·76; OCH_3, 0·0 per cent; mol. wt. (perchloric acid titration), 472.

Neomethymycin solvates rather readily and when crystallized from aqueous acetone it yielded 1 cm long crystals of the acetone solvate, m.p. 156–158° with loss of solvent near 100°. A very characteristic solvate is that formed with methylene dichloride, and this serves very satisfactorily for the preparative isolation of neomethymycin from methymycin mother liquors by the following simple procedure. The crude antibiotic concentrate was dissolved in warm methanol and evaporated to a foam on the steam bath *in vacuo*, and methylene dichloride was added while still hot. The mixture was swirled until all dissolved and upon cooling colorless crystals of the methylene dichloride solvate separated. These were filtered off and treated twice more by the above scheme, and the combined mother liquors were then subjected to chromatography to recover methymycin. The neomethymycin–methylene dichloride solvate formed large hexagonal plates, m.p. 154–156°, with gas given off near 135–140°, $[\alpha]_D$ +66° (EtOH). *Anal.* Calcd. for $C_{25}H_{43}NO_7 \cdot CH_2Cl_2$: C, 56·32; H, 8·18; Cl, 12·79; mol. wt., 554·5. Found: C, 57·05; H, 8·02; Cl, 11·95 per cent; mol. wt. (perchloric acid titration), 545.

Hydrogenation of neomethymycin (II). The hydrogenation of 225 mg of neomethymycin–methylene dichloride solvate was conducted at 30° and atmospheric pressure in 5 ml of ethanol with 40 mg of 5% palladized charcoal catalyst. Hydrogen consumption stopped after 1·1 equivalents had been consumed, the catalyst was filtered off, the filtrate evaporated to dryness and the residue was crystallized from hexane–methylene dichloride. The resulting *dihydroneomethymycin–methylene dichloride* solvate (75 per cent yield) had no definite melting point, solvent being lost near 100°, $[\alpha]_D$ +3°. *Anal.* Calcd. for $C_{25}H_{45}NO_7 \cdot CH_2Cl_2$: Cl, 12·74. Found: Cl, 12·90 per cent. *Anal.* Calcd. for $C_{25}H_{45}NO_7$: C, 63·66; H, 9·62; N, 2·97. Found after drying at 100° and high vacuum to constant weight: C, 63·83; H, 9·60; N, 3·02 per cent; loss in weight: 15·23.

Isolation of desosamine (III). A solution of 200 mg of neomethymycin (II) in 5 ml of 5 N hydrochloric acid was heated on the steam bath for 15 min and extracted with chloroform, and the aqueous solution was evaporated to dryness *in vacuo*. The crude crystalline desosamine hydrochloride (95 mg) was recrystallized three times from methanol–acetone, whereupon it melted at 186–188° (dec.), undepressed upon admixture with desosamine hydrochloride obtained[4] from methymycin (I). The infrared spectra of both specimens in potassium bromide pellets were identical.

Isolation of acetaldehyde. Neomethymycin (II) did not consume any reagent when left for 4 hr at room temperature with 0·1 N aqueous solution of periodic acid, thus showing that the glycol system was blocked.

A solution of 300 mg of neomethymycin (II) and 400 mg of lithium aluminum hydride in 25 ml of dry ether was heated under reflux for 18 hr and the excess of reagent decomposed with ethyl acetate. After addition of a few milliliters of a saturated aqueous solution of sodium sulfate, the mixture was dried over anhydrous sodium sulfate and filtered, and the inorganic salts extracted thoroughly with chloroform. The combined filtrate and extracts were evaporated to dryness, benzene was added and the evaporation was repeated. The gummy residue (240 mg) exhibited only a trace of carbonyl band in the infrared region and to its aqueous solution was added 25 ml of

0·1 N periodic acid solution. The uptake of reagent stopped within 15 min (1·2 equivalents) and the solution was steam distilled into excess of 2,4-dinitrophenylhydrazine dissolved in sulfuric acid. The precipitate (125 mg) was collected and recrystallized from aqueous ethanol to yield 55 mg of yellow needles of acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 166–168°. Identity was established by mixture melting-point determination, infrared spectra, comparison with an authentic sample and paper-chromatographic analysis in two systems* in which acetaldehyde and propionaldehyde 2,4-dinitrophenylhydrazones are separated easily. *Anal.* Calcd. for $C_8H_8N_4O_4$: C, 42·86; H, 3·60; N, 24·99. Found: C, 43·28; N, 3·65; N, 24·32 per cent.

Acetaldehyde was also isolated when the lithium aluminum hydride reduction product was oxidized with a 0·2 N aqueous solution of sodium metaperiodate.

Alternatively, a sample (ca. 200 mg) of neomethymycin (II), dihydroneomethymycin or dihydroneomethynolide (XXVI) was dissolved in 5 ml each of ethanol and of 2 N aqueous sodium hydroxide, warmed for 30 min at 70° and set aside at 25° for 2 hr; the pH was adjusted to 6·8 with hydrochloric acid and 25 ml of 0·1 N sodium metaperiodate solution were added. After standing overnight, the mixture was subjected to steam distillation and 30–54 per cent of acetaldehyde 2,4-dinitrophenylhydrazone was isolated.

Sulfuric acid cleavage of neomethymycin (II). A solution of 200 mg of neomethymycin in 10 ml of 5 N sulfuric acid was boiled for 10 min, cooled rapidly, saturated with ammonium sulfate and extracted with ether. Evaporation of the ether solution left a colorless oil, which could be crystallized from *wet* ether to furnish up to 35 per cent of *neomethynolide hydrate*, m.p. 95–110°. The mother liquors were dissolved in benzene–ether (1 : 1) and passed through a short column of alumina deactivated with acetic acid. Elution with benzene–ether mixtures and ether furnished nearly 60 per cent of cyclo*neomethynolide* as an oil, while remaining traces of neomethynolide were only removed with ether containing 2 per cent of methanol. The separation of the two cleavage products by chromatography was quite sharp and was utilized also in larger scale experiments.

Neomethynolide (XIX). Recrystallization of neomethynolide hydrate from wet ether–hexane or aqueous acetone yielded long, slender needles with a variable melting point range between 90–120°, $[\alpha]_D$ + 99°. *Anal.* Calcd. for $C_{17}H_{28}O_5 \cdot H_2O$: C, 61·79; H, 9·15; 5 C-CH_3, 22·75; H_2O, 5·45. Found: C, 62·65; H, 9·08; C-CH_3, 21·74 per cent. After drying at 100° in high vacuum: loss in weight, 5·63; C, 65·81; H, 8·99 per cent.

The substance could be rendered anhydrous by sublimation of the hydrate at 130–140° at 0·005 mm or by co-distillation with benzene followed by crystallization from benzene–hexane mixture, m.p. 186–187°, $[\alpha]_D$ +108°, λ_{max}^{EtOH} 227·5 mμ (log ε 4·10), $\lambda_{max}^{CHCl_3}$ 2·93, 5·75, 5·90 and 6·10 μ. *Anal.* Calcd. for $C_{17}H_{28}O_5$: C, 65·36; H, 9·03. Found: C, 65·61; H, 9·02 per cent.

Neomethynolide diacetate (XX). This was obtained as colorless needles by acetylating neomethynolide hydrate with acetic anhydride–pyridine overnight at room temperature and recrystallizing from aqueous acetone, m.p. 199–201°, depressed to 160–190° upon admixture with methynolide mono-acetate (V), $[\alpha]_D$ +84°, $\lambda_{max}^{CHCl_3}$ 5·71, 5·88 and 6·08 μ. *Anal.* Calcd. for $C_{21}H_{32}O_7$: C, 63·61; H, 8·14; acetyl, 21·71. Found: C, 63·90; N, 8·04; acetyl, 22·29 per cent.

* We are indebted to Dr. K. Murai (Research Laboratories, Chas. Pfizer and Co.) for this analysis.

Neomethynolide did not react with periodic acid, but when it was first reduced with lithium aluminum hydride as described above (except that tetrahydrofuran was used as solvent instead of ether) for neomethymycin (II) and then treated with an aqueous solution of periodic acid, 0·9 equivalents were consumed in ca. 30 min. Steam distillation into 2,4-dinitrophenylhydrazine solution and recrystallization furnished 30 per cent of pure acetaldehyde 2,4–dinitrophenylhydrazone with m.p. 168–169°. The infrared spectrum showed the characteristic band at 11·40 μ (chloroform), which is not present in propionaldehyde 2,4-dinitrophenylhydrazone. *Anal.* Calcd. for $C_8H_8N_4O_4$: C, 42·86; H, 3·60; N, 24·99. Found: C, 43·02; H, 3·75; N, 25·27 per cent.

In order to examine the possibility of eliminating the hydroxyl group involved in lactone formation, a solution of 200 mg of neomethynolide (XIX) in 5 ml of ethanol was diluted with 5 ml of 4 N aqueous sodium hydroxide solution and left at room temperature. Immediate ultraviolet spectroscopic examination showed the presence of the 227·5 mμ peak, but within 2 hr this had disappeared and a maximum at 280 mμ (log ε 3·23) was noted. After 18 hr at room temperature, no ultraviolet selective absorption was left, possibly owing to alkaline cleavage. In a second experiment, a solution of 188 mg of neomethynolide (XIX) in 10 ml of absolute ethanol containing 2·5 equivalents of sodium was left at room temperature and the ultraviolet absorption was examined at 2 hr intervals. The intensity of the 227·5 mμ maximum was reduced as the 280 mμ band started to appear and after standing overnight only a maximum at 280 mμ was noticeable. Its low extinction (log ε 3·34) indicated, however, that formation of the dienone acid (XXV) had to compete with other reactions involving the unsaturated carbonyl chromophore and no pure product was isolated from this mixture.

Dihydroneomethynolide (XXVI). Quantitative micro-hydrogenation of neomethynolide (XIX) in acetic acid–ethanol (2 : 1) at 0° with platinum oxide resulted in the uptake of 1·93 molar equivalents of hydrogen. Consequently in a preparative experiment with 165 mg of neomethynolide (XIX), the hydrogenation was carried out in absolute ethanol with 100 mg of 5% palladized charcoal catalyst and hydrogen consumption corresponding to one equivalent stopped after 15 min. Filtration of the catalyst, evaporation of the filtrate to dryness and recrystallization from ether–hexane gave in nearly quantitative yield heavy prisms of dihydroneomethynolide (XXVI), which exhibited m.p. 134–136°, $[\alpha]_D$ −43° (dioxane), $\lambda_{max}^{CHCl_3}$ 2·80, 2·90, 5·77 and 5·85 μ, rotary dispersion (Fig. 2) in dioxan (*c*, 0·023) : $[\alpha]_{700}$ −61°, $[\alpha]_{589}$ −61°, $[\alpha]_{400-350}$ −70° (infl), $[\alpha]_{320}$ −180°, $[\alpha]_{307·5}$ +17°, $[\alpha]_{285}$ −200°. *Anal.* Calcd. for $C_{17}H_{30}O_5$: C, 64·94; H, 9·62. Found: C, 64·67; H, 9·43 per cent.

The rotation of a dioxan solution of the substance did not change for 24 hr in the presence of 2 drops of concentrated sulfuric acid and the product was recovered unchanged upon sublimation at 130–140° and 0·01 mm.

A 120 mg sample of dihydroneomethynolide (XXVI) was reduced with lithium aluminum hydride in tetrahydrofuran for 24 hr and the crude total reduction product was dissolved in 25 ml of purified dioxan and treated with a solution of 112·5 mg of sodium metaperiodate in 5 ml of water. After the mixture had been standing for 30 min, the acetaldehyde was removed by steam distillation, and the solution was cooled and titrated against a blank that had been put through the same steps except for the absence of dihydroneomethynolide; 0·76 molar equivalents of reagent had been

consumed. The solution was then saturated with sodium chloride, extracted with ether continuously overnight and then evaporated to dryness. The residual oil was taken up in 5 ml of dioxan, concentrated to 2 ml, mixed with 5 ml of 10% sodium hydroxide solution and treated with a solution of 1 g of iodine and 2 g of potassium iodide in 8 ml of water. After being warmed for 2 min at 60°, the solution was decolorized by the addition of a few drops of 10% sodium hydroxide solution, poured into water and set aside. No iodoform was obtained, thus excluding definitely the location of a methyl group at C-11 as in (VII).

Ozonolysis of neomethynolide (XIX). Ozone was passed at −80° through a solution of 250 mg of neomethynolide (XIX) in 20 ml of ethyl acetate until a permanent blue color was obtained (ca. 30 min). The resulting solution was added dropwise to a mixture of 25 ml of 10% sodium hydroxide and 8 ml of 30% hydrogen peroxide, stirred at room temperature for 1 hr and then heated until all ethyl acetate had been removed. The aqueous solution was acidified with concentrated hydrochloric acid, set aside for 15 min and then saturated with sodium chloride. Ether extraction afforded an oil still containing acetic acid and the latter was removed by distillation *in vacuo* on a steam-bath. Three recrystallizations of the residue from ether–hexane afforded 40 mg of analytically pure lactonic acid (XI), m.p. 125–126°, $[\alpha]_D$ +42°, +43°. Its infrared spectrum in a potassium bromide pellet was identical with that of a specimen derived[6] from methymycin (I). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59·98; H, 8·05; mol. wt., 200·2. Found: C, 59·77; H, 7·78 per cent; neut. equiv., 195 (immediate titration), 97 (back titration after standing in excess of base).

Similar treatment* of methynolide (IV) (0·5 g) in 40 ml of ethyl acetate at −70°, followed by decomposition of the ozonide with alkaline hydrogen peroxide (1 hr at 25°, then sodium hydroxide pellets were added and the mixture was boiled for 1 hr) and continuous ether extraction gave 0·45 g of viscous oil. Careful crystallization from ether–hexane provided 200 mg of the lactonic acid (XI), m.p. 123–127°.

cyclo*Neomethynolide* (XXII). The substance, obtained above in the sulfuric acid cleavage of neomethymycin (II), could not be crystallized, but its homogeneity was established by repeated chromatography and conversion of the first and last eluates to the crystalline mono-acetate (XXIII). An analytical sample of *cyclo*neomethynolide (XXII) was prepared by taking a middle chromatogram fraction and distilling it at 140°/0·01 mm $[\alpha]_D$ −40°, no selective high ultraviolet absorption, $\lambda_{max}^{CHCl_3}$ 2·90, 5·72, 5·83 and sharp band at 9·01 μ [absent in both (XIX and XXVI)], rotary dispersion (Fig. 2) in dioxan (*c*, 0·127) : $[\alpha]_{700}$ −45°, $[\alpha]_{589}$ −48°, $[\alpha]_{320}$ −460°, $[\alpha]_{295}$ +51°, $[\alpha]_{280}$ −196°. *Anal.* Calcd. for $C_{17}H_{28}O_5$: C, 65·36; H, 9·03. Found: C, 65·48; H, 9·00 per cent.

Reduction with lithium aluminum hydride followed by treatment with aqueous periodic acid did not result in any appreciable consumption of reagent over a 6 hr period.

Acetylation with acetic anhydride–pyridine and recrystallization from aqueous methanol afforded cyclo*neomethynolide* 3-*acetate* (XXIII) as colorless prisms, m.p. 194° (with crystal change and sublimation from 175°), $[\alpha]_D$ +1°, $\lambda_{max}^{CHCl_3}$ 5·69, 5·83 and 8·05 μ, but no hydroxyl absorption. *Anal.* Calcd. for $C_{19}H_{30}O_6$: C, 64·38; H, 8·53; acetyl, 12·13. Found: C, 64·64; H, 8·16; acetyl, 11·93 per cent.

Attempted micro-hydrogenation in ethanol solution with either palladium–charcoal or platinum oxide did not result in any hydrogen uptake.

* This experiment was carried out by Mr. J. Kutney.

Dehydrocycloneomethynolide (XXIV). Oxidation of 87 mg of *cyclo*neomethynolide (XXII) in acetone solution at 5–10° with one equivalent of chromium trioxide–sulfuric acid solution[16] was complete in 2–3 min, whereupon the green solution was poured into a saturated solution of ammonium sulfate and extracted continuously with ether. The ether-soluble material was filtered in benzene solution through a very short column of alumina deactivated with acetic acid and the eluted product was recrystallized from light petroleum ether to yield 67 mg of heavy prisms, m.p. 122–124° (with sublimation), $[\alpha]_D$ +60°. *Anal.* Calcd. for $C_{17}H_{20}O_5$: C, 65·78; H, 8·44. Found: C, 65·94; H, 8·30 per cent.

A 64 mg sample of this ketone was subjected to base treatment, followed by acidification exactly as described earlier[6] for dehydromethynolide and yielded 5·77 mg (63·5 per cent) of carbon dioxide.*

Iodoform tests. The following procedure was used in determining the presence of a potential methyl ketone function. A few milligrams of substance, dissolved in 0·5 ml of purified dioxan, was mixed with 0·25 ml of 10% aqueous sodium hydroxide and to it was added dropwise a solution of 1 g of iodine and 2 g of potassium iodide in 8 ml of water until a deep red-brown color remained. After the solution had been heated for 1 min at 60°, 2 drops of 10% aqueous sodium hydroxide was added to remove excess of iodine, and the solution was cooled and diluted with much water. The resulting precipitate of iodoform was sublimed at 100°/40 mm, whereupon the yellow crystals melted at 124° (dec.). Under those conditions, neomethynolide (XIX) and dihydroneomethynolide (XXVI) yielded iodoform, while *cyclo*neomethynolide (XXII) and methynolide (IV) did not respond.

Rotatory dispersion of pikromycin (XXVII). Rotary dispersion (Fig. 1) in dioxan solution (ca. 0·125) on sample provided by Prof. H. Brockmann (University of Göttingen): $[\alpha]_{700}$ −14°, $[\alpha]_{589}$ −15°, $[\alpha]_{350}$ −171°, $[\alpha]_{320}$ +333°, $[\alpha]_{285}$ 0°.

Rotatory dispersion of tetrahydrokromycin (XXVIII). Rotary dispersion (Fig. 2) in dioxan solution (ca. 0·095) on sample provided by Dr. R. Anliker (E.T.H., Zürich): $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +102°, $[\alpha]_{312\cdot5}$ +2300°, $[\alpha]_{280}$ −1560°.

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* We are indebted to Mr. Joseph F. Alicino for this determination.

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THE EXTRACTIVES OF *VITEX LUCENS*—I

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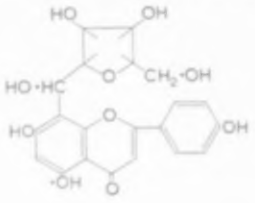
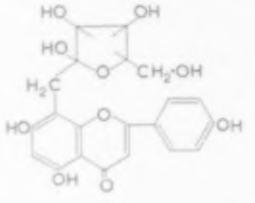
Abstract—Vitexin, isolated from *Vitex lucens*, has been formulated as $C_{21}H_{20}O_{10}$ and, in agreement with recent workers, structure (I) has been assigned to the compound. β-sitosterol has been isolated from the heartwood.

EVANS *et al.*[1] have advanced the tentative structure (I) for vitexin, isolated from New Zealand puriri wood (*Vitex lucens**).

Working on similar lines, we have arrived at the same structure for this compound. The formulation of vitexin as $C_{21}H_{20}O_{10}$ has been confirmed by the preparation of



(I)



(II)

the hepta-acetate, a hexa-acetate, a tetrabenzoate, the trimethyl and triethyl derivatives, a diethyl derivative, a ditosylate and a monotrityl derivative. Repetition of the degradative studies of previous workers[2–6] resulted, in the main, in identical products. Only those that are new or differ markedly from those of previous workers are described in this communication.

In contrast to the isolation by Evans *et al.*; vitexin has only been obtained from the wood extracts after acid hydrolysis. It is considered by us to be an artifact formed during hydrolysis, which requires conditions of aerial oxidation for the production of good yields. The view that vitexin from saponarin is also an artifact has been expressed by Geissman *et al.*[7,8] Vitexin was obtained from both the sapwood and heartwood of *Vitex lucens* by a modification of Perkin's method,[2] but not from the leaves by the same procedure. The trimethyl and triethyl derivatives were each prepared by extended heating under reflux with dimethyl sulphate or diethyl sulphate, respectively, and anhydrous potassium carbonate in acetone. These derivatives have previously been prepared from vitexin penta-acetate.[1]

As Evans *et al.* have shown, oxidation of vitexin with sodium periodate gave variable and apparently anomalous results. The initial stages of reaction showed the comparatively rapid initial uptake of 2 molecules of periodate followed by further

* Formerly *Vitex littoralis;* see Cheeseman.

[1] W. H. Evans, A. McGookin, L. Jurd, A. Robertson and W. R. N. Williamson, *J. Chem. Soc.* 3510 (1957).
[2] A. G. Perkin, *J. Chem. Soc.* **73**, 1019 (1898).
[3] A. G. Perkin, *J. Chem. Soc.* **77**, 422 (1900).
[4] G. Barger, *J. Chem. Soc.* **89**, 121 (1906).
[5] E. Péteri, *J. Chem. Soc.* 1635 (1939).
[6] T. Nakaoki, *J. Pharm. Soc. Japan* **64**, 57 (1944).
[7] T. A. Geissman and U. Krannen-Fielder, *Naturwissenschaften* **10**, 226 (1956).
[8] T. A. Geissman, L. Jurd and M. K. Seikel, *Arch. Biochem. Biophys.* **67**, 284 (1957).
[9] T. F. Cheeseman, *Manual of New Zealand Flora* (2nd Ed.) p. 763. Government Printer, New Zealand (1925).

gradual oxidation and is thus not confined to 1:2-diol fission. Small amounts of a volatile acid formed on oxidation and reported by Evans *et al.* were identified by us as formic acid (S-benzyl*iso*thiuronium salt), but this is regarded as a product of secondary oxidation during the formation of 8-formylapigenin from dehydro*seco*-vitexin, and not as evidence for the acceptance of these workers' alternative structure (II).

In contrast to Nakaoki's claim[6] to have isolated 2:4:6-trihydroxyphenylacetic acid, alkaline permanganate oxidation of vitexin led to the formation of apigenin, probably arising from the ready decarboxylation of apigenin-8-carboxylic acid. The failure to isolate Nakaoki's reported product lends further evidence to the acceptance of structure (I) for vitexin. Nakaoki, in assigning a 2:3:4:5:6-pentahydroxy-*n*-hexyl structure for the non-flavonoid moiety of vitexin, reported that it formed a diacetone compound. Repeated attempts to form an *iso*propylidene derivative however, have been unsuccessful. This could be attributed to a *trans*-diol grouping in the $C_6H_{11}O_5$ residue of (I).

Perkin's "homovitexin" has now been shown to be a dextrorotatory compound, m.p. 246–247°, isomeric with vitexin, for which the name *iso*vitexin is now preferred. Although a comprehensive examination of *iso*vitexin was not possible owing to its formation in low yield (0·04 per cent), it could be readily differentiated from vitexin by its greater solubilities and by paper chromatography in two solvent systems. *iso*Vitexin formed a hepta-acetate with acetic anhydride and pyridine, but, as with vitexin, difficulty was encountered in the attempted formation of a trimethyl derivative. The products of alkaline fusion were phloroglucinol, *p*-hydroxybenzoic acid and acetic acid.

Paper chromatography of the crude aglycone mixtures of a series of hydrolyses has now shown that *iso*vitexin is the initial product in the formation of vitexin. Further extended acid treatment of *iso*vitexin gave a good yield of vitexin. Also the yield of *iso*vitexin from hydrolysis of the original wood extract depended on the acid concentration and the time of heating, high acid concentration and extended hydrolysis resulting in the production of negligible quantities of *iso*vitexin. This behaviour is paralleled by Nakaoki's findings for acid treatment of saponarin. Although the melting point of *iso*vitexin is somewhat higher than that recorded for saponaretin[6] (m.p. 225–226°) and a positive rotation was observed for *iso*vitexin, it appears likely that the two compounds could be identical. Seikel and Geissman[10] have shown by paper chromatography that an equilibrium exists between vitexin and saponaretin in hot acid solution, and with the assumption that saponaretin is represented by the formula $C_{21}H_{22}O_{11}$, have suggested that the equilibrium might be explained as a cyclisation by dehydration and ring opening by hydration.

A crystalline sterol isolated from a light petroleum extract of the heartwood was identified as *β*-sitosterol.

EXPERIMENTAL

β-Sitosterol. Coarsely ground heartwood of *Vitex lucens* (14·5 kg) was extracted in a Soxhlet extractor with light petroleum (boiling range 50–65°) for 24 hr. Trituration of the concentrated extract with acetone and then chromatography of the waxy solid (1·0 g) in benzene on alumina gave *β*-sitosterol (plates from methanol), m.p. and mixed m.p. 136–137°, λ_{max} 208 mμ (log ε 3·72). The infra-red spectrum was

[10] M. K. Seikel and T. A. Geissman, *Arch. Biochem. Biophys.* **71**, 17 (1957).

identical with that recorded[11] (Found: C, 84·2; H, 11·5. Calc. for $C_{29}H_{50}O$: C, 84·0; H, 12·1 per cent). The acetate had m.p. and mixed m.p. 127–128° (Found: C, 82·3; H, 11·3. Calc. for $C_{31}H_{52}O_2$: C, 81·5; H, 11·5 per cent).

Vitexin. Finely milled sapwood (8·2 kg) was extracted with ethanol for 36 hr and the concentrated extract was separated from insoluble material by water extraction. The concentrated aqueous solution was heated under reflux with 1% hydrochloric acid in an open dish for 1 hr. A greenish-black polymer was deposited on heating and it was separated by repeated filtration of the hot solution. Hydrolysis was then continued with an increased acid concentration (2%) for 2 hr. Crude vitexin (2·0 per cent yield) was obtained as a microcrystalline mass by washing the tarry deposit several times with ethanol. Vitexin (1·5 per cent yield) was also obtained from an acetone extract of the heartwood by the same procedure. Paper chromatography of the concentrated hydrolysate with butanol–pyridine–water (3:1:1) showed the presence of glucose. The polymer on alkaline and acid treatment had an identical infra-red spectrum with that obtained from either asperuloside or toluquinhydrone, on similar treatment.[12]

Vitexin crystallised from 60% acetic acid in yellow rhombic plates, m.p. 263° (dec.), $[\alpha]_D^{18}$ −14·3° (*c.* 1·10 in pyridine), λ_{max} 270 and 335 mμ (log ε 4·32 and 4·33), infra-red spectrum (potassium bromide disc method) 3425, 3392, 3284, 2889, 1650 cm^{-1} (Found for sample dried over magnesium perchlorate: C, 58·5; H, 5·1. Calc. for $C_{21}H_{20}O_{10}$: C, 58·3; H, 4·7 per cent).

Vitexin hepta-acetate. Acetylation with acetic anhydride (6 hr at 100°) gave the hepta-acetate, which separated from ethanol–acetic acid as colourless rhombs, with a negative ferric chloride reaction, m.p. 255–256°, $[\alpha]_D^{18}$ −75·7° (*c.* 0·95 in ethanol), λ_{max} 225 and 300 mμ (log ε 4·21 and 4·28), infra-red spectrum 1748, 1712, 1656 cm^{-1} (Found: C, 57·7; H, 4·6; Ac, 41·5, 41·9. Calc. for $C_{35}H_{34}O_7$: C, 57·85; H, 4·7; 7Ac, 41·5 per cent).

Vitexin hexa-acetate. Acetylation of vitexin (450 mg) with acetic anhydride (1·5 g) and fused sodium acetate (2·0 g) for 8 hr at 100° gave a brown oil, which solidified on being kept overnight. The hepta-acetate (20 mg), m.p. and mixed m.p. 255–256°, was separated by crystallisation of the crude product from ethanol–acetic acid. *Vitexin hexa-acetate* (520 mg) was deposited when the mother-liquors were poured into water. The product separated from absolute ethanol as colourless needles, m.p. 157–159°, λ_{max} 271 and 305 mμ (log ε 4·49 and 4·36), infra-red spectrum 3509, 3135, 2959, 1754, 1656 cm^{-1} (Found: C, 57·4; H, 5·1; Ac, 37·9. $C_{33}H_{32}O_{16}$ requires C, 57·9; H, 4·7; 6Ac, 37·7 per cent). The derivative was soluble in cold sodium hydroxide and gave a dark-red reaction with ferric chloride. Further acetylation with acetic anhydride (6 hr at 100°) gave vitexin hepta-acetate, m.p. and mixed m.p. 255–256°.

Vitexin tetrabenzoate. Excess of benzoyl chloride was added in portions with shaking and cooling to vitexin in 10% sodium hydroxide. The product, isolated as a cream oil, solidified on standing. Purification by chromatography in benzene on neutralized alumina and crystallisation from benzene–ligroin gave colourless needles of the *tetrabenzoate*, m.p. 137°, with a negative ferric chloride reaction, infra-red spectrum 3497, 3135, 3003, 1793, 1653 cm^{-1} (Found: C, 69·0; H, 4·3; Bz, 49·1. $C_{49}H_{36}O_{14}$ requires C, 69·3; H, 4·2; 4Bz, 49·5 per cent).

[11] R. M. Ma and P. S. Schaffer, *Arch. Biochem. Biophys.* **47**, 419 (1953).
[12] L. H. Briggs and B. F. Cain, *J. Chem. Soc.* 4182 (1954).

Ditosylvitexin. A cooled solution of toluene-*p*-sulphonyl chloride (320 mg) in pyridine (2 ml) was added dropwise, with mechanical stirring, to vitexin (161 mg) in the same solvent at −10°C. After 2 hr at −10° and 5 days at room temperature, the *ditosyl derivative* (190 mg) was precipitated on contact with crushed ice. Repeated crystallisation from methanol gave short cream rods, m.p. 198° (dec.), infra-red spectrum 3425, 2959, 2717, 1653 cm^{-1} (Found: C, 56·3; H, 4·3. $C_{21}H_{20}O_{10}$ $(C_7H_6O_2S)_2$ requires C, 56·7; H, 4·35 per cent).

Monotritylvitexin. A cooled solution of triphenylmethyl chloride (180 mg) in dry pyridine (2 ml) was added, with mechanical stirring, over a period of 30 min to vitexin (156 mg) in the same solvent (2 ml) at −10°C. After 2 hr at −10° and 12 days at room temperature, the derivative (330 mg) was precipitated as a cream amorphous powder on contact with crushed ice. Three crystallisations from methanol gave a cream microcrystalline *monotrityl derivative* (102 mg), m.p. 234–235° (dec.) with shrinking at 190°, infra-red spectrum 3448, 3115, 2959, 1656 cm^{-1} (Found for sample dried at 100°: C, 70·8; H, 5·3. $C_{40}H_{34}O_{14}$ requires C, 71·2; H, 5·1 per cent).

5:7:4′-*Trimethylvitexin.* A suspension of finely powdered vitexin (500 mg) in dry acetone (40 ml), was heated under reflux with dimethyl sulphate (1·9 ml) and anhydrous potassium carbonate (3·43 g) for 86 hr. Concentration of the combined filtrate and the hot acetone washings of the salts gave 5:7:4′-trimethylvitexin as an amorphous yellow mass (35 per cent). Crystallisation from methanol gave clusters of colourless needles, m.p. 195–196° (dec.), with a negative ferric chloride reaction, insoluble in cold aqueous sodium hydroxide, λ_{max} 265 and 312 mμ (log ε 4·71 and 4·61) infra-red spectrum 3401, 2950, 1647 cm^{-1} (Found: C, 61·0; H, 5·4; OMe, 18·0. Calc. for $C_{24}H_{26}O_{10}$: C, 60·8; H, 5·5; 3OMe, 19·6 per cent). Trimethylvitexin, m.p. and mixed m.p. 195–196°, was also obtained in higher yield (50 per cent) by initial treatment of vitexin in absolute methanol with ethereal diazomethane and then further methylation of the crude product by the method described above.

The tetra-acetate, prepared with acetic anhydride–pyridine (6 hr at 100°) separated from 75% aqueous ethanol as colourless needles, m.p. 208°, λ_{max} 265 and 328 mμ (log ε 4·44 and 4·48), infra-red spectrum 2959, 2841, 1754, 1698, 1647 cm^{-1} (Found: C, 59·9; H, 5·7; Ac, 26·1; OMe, 14·1. Calc. for $C_{32}H_{34}O_{14}$: C, 59·8; H, 5·3; 4Ac, 26·8; 3OMe, 14·5 per cent).

7:4′-*Diethylvitexin.* A mixture of finely powdered vitexin (1·0 g), diethyl sulphate (1·5 ml) and potassium carbonate (3·6 g) was heated under reflux with acetone (50 ml) for 48 hr. Evaporation of the acetone solution and washings yielded a gum, which was triturated with water. The residue (710 mg), when repeatedly crystallised from ethanol, gave 7:4′-*diethylvitexin* (62 per cent) as pale-yellow needles, m.p. 276–276·5°, λ_{max} 270 and 326 mμ (log ε 4·26 and 4·21), infra-red spectrum 3413, 2941, 1656 cm^{-1} (Found: C, 61·0, 60·9; H, 6·1, 6·0; OEt, 18·85. $C_{25}H_{28}O_{10}$ requires C, 61·5; H, 5·8; 2OEt, 18·4 per cent). Diethylvitexin was soluble in 10% sodium carbonate and gave a red coloration with ferric chloride.

5:7:4′-*Triethylvitexin.* Continued ethylation of diethylvitexin gave the 5:7:4′-triethyl derivative as a yellow gum after removal of excess of diethyl sulphate with light petroleum. It separated from methanol as colourless needles, m.p. 270° (lit.[1] m.p. 270°), with a negative ferric chloride test. Triethylvitexin was also the major product (500 mg from 1 g) from prolonged ethylation (68 hr) of vitexin.

Treatment of crude triethylvitexin with acetic anhydride and fused sodium

acetate at 100° for 8½ hr gave the tetra-acetate, which separated from ethanol as colourless needles, m.p. 235·5°, with sintering at 120° (Found: C, 61·2; H, 5·7; Ac, 26·6; OEt, 18·7. Calc. for $C_{35}H_{40}O_{14}$: C, 61·4; H, 5·9; 4Ac, 25·2; 3OEt, 19·7 per cent).

Alkaline permanganate oxidation of vitexin. Potassium permanganate (535 mg) was added in portions, with stirring, to vitexin (646 mg) in 0·4% sodium hydroxide (25 ml) at room temperature. Stirring was continued for 13 hr, the mixture was set aside overnight, and the reaction was stopped by addition of methanol. Precipitated manganese dioxide was removed and most of the ethanol was removed by distilling under reduced pressure. Acidification gave a yellow precipitate (344 mg), m.p. 246° (dec.), which, after being washed with water and hot ether, on slow crystallisation from ethanol gave apigenin as a yellow microcrystalline powder, m.p. and mixed m.p. 347° (dec.), λ_{max} 269 and 335 mμ (log ε 4·30 and 4·32) (Found for sample dried at 100°: C, 60·2; H, 4·6. Calc. for $C_{15}H_{10}O_5 \cdot 1{\cdot}5H_2O$: C, 60·6; H, 4·4 per cent). The product gave solubility and colour reactions identical with those of an authentic sample.

The triacetate, prepared with acetic anhydride–pyridine (2 hr at 100°) crystallised as colourless needles from methanol, m.p. and mixed m.p. 180–181°.

Ether extraction of the acid filtrate gave an orange gum on removal of the solvent. From the benzene extract of the residue *p*-hydroxybenzoic acid (needles from ether), m.p. and mixed m.p. 209–210°, was isolated in low yield (10 mg).

iso*Vitexin.* *iso*Vitexin, obtained from the alcoholic washings of vitexin by the method of Perkin,[2] crystallised from absolute ethanol as yellow needles, m.p. 246–247° (dec.) (lit.,[2] m.p. 245–246° for "homovitexin"), $[\alpha]_D^{30}$ + 16·21° (*c.* 0·37 in ethanol), λ_{max} 270 and 337 mμ (log ε 4·43 and 4·40), infra-red spectrum 3378, 2959, 1661 cm^{-1} (Found: C, 58·7; H, 5·1. $C_{21}H_{20}O_{10}$ requires C, 58·3; H, 4·7 per cent). Solubility properties and colour reactions corresponded with those recorded for "homovitexin".[2]

iso*Vitexin hepta-acetate.* Acetylation with acetic anhydride–pyridine (2 hr at 100°) gave the *hepta-acetate*, which separated from ethanol as colourless prisms, m.p. 248°, with a negative ferric chloride reaction, infra-red spectra 1773, 1712, 1661 cm^{-1} (Found: C, 57·6; H, 5·0; Ac, 42·2. $C_{35}H_{34}O_{17}$ requires C, 57·85; H, 4·7; 7Ac, 41·5 per cent).

Conversion to vitexin. An ethanolic solution of *iso*vitexin (50 mg) was heated under reflux with 5% sulphuric acid for 8 hr. The brown solid (41 mg) obtained on dilution gave vitexin (rhombic plates from 60% acetic acid), m.p. and mixed m.p. 262–263°.

Paper chromatography. Chromatography on Whatman No. 1 paper with "Forestal solvent"[13] and butanol–acetic acid–water (4:1:5) gave the following R_F values: vitexin, 0·83 and 0·65; *iso*vitexin, 0·90 and 0·76. The spots were coloured brown-purple in ultra-violet light and yellow-green in the presence of ammonia.

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UEBER DERIVATE DER D-XYLOSE

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Zusammenfassung—1:2-*iso*Propyliden-D-xylose wird durch Mesylierung, Umsatz mit Ammoniak und anschliessende alkalische Verseifung in die 1:2-*iso*Propyliden-5-deoxy-5-amino-D-xylose übergeführt, die selbst und als Methansulfonsaures Salz kristallin erhalten wurde.

FÜR die 1:2-*iso*Propyliden-D-xylose[1] (Monoaceton-D-xylose) (I) wurde eine verbesserte Darstellung ausgerbeitet. Die Kondensation dieser Verbindung mit einem Mol. Methansulfonsäurechlorid (Mesylchlorid) in Pyridin ergab die 1:2-*iso*Propyliden-5-mesyl-D-xylose. (II), die Behandlung mit zwei oder mehr Mol. Mesylchlorid die 1:2-*iso*Propyliden-3:5-dimesyl-D-xylose (III), beide kristallin und in guter Ausbeute.

Aus der Dimesylverbindung werden die Mesylgruppen bei höherer Temperatur (100°) durch wässrige KOH abgespalten aber unter gleichzeitiger Zersetzung. Alkoholische KOH führt in guter Ausbeute zu der—schon früher beschriebenen[2]—1:2-*iso*Propyliden-3:5-anhydro-D-xylose (IV). Der merkwüridge Vierring in dieser Substanz wird durch wässrige NaOH oder KOH in der Hitze ohne Waldensche Umkehrung zur Monoaceton-D-xylose aufgespalten.

Bei der Behandlung der Dimesylverbindung mit NH_3 in Methanol bei 100° wird der 5-ständige (primäre) Mesoxylrest durch $—NH_2$ ersetzt. Die 1:2-*iso*Propyliden-3-mesyl-5-deoxy-5-amino-D-xylose (V) konnte kristallin in guter Ausbeute sowohl als methansulfonsaures Salz wie als frei Base gewonnen werden. Die 3-Mesylgruppe liess sich durch KOH in Methanol abspalten. Mam erhält so die 1:2-*iso*Propyliden-5-deoxy-5-amino-D-xylose (VI) ohne Schwierigkeit in kristalliner Form, als methansulfonsaures Salz oder als freie Base. Auf etwas anderem Wege war sie schon früher hergestellt wordden, allerdings nicht kristallin.[3]

Die gleiche Verbindung (VI) wird aus der 1:2-*iso*Propyliden-5-mesyl-D-xylose (II) ebenfalls mit NH_3 in Methanol gewonnen.

Der Deutschen Forschungsgemeinschaft danken wir auch an dieser Stelle für ihre Unterstützung dieser Arbeit.

VERSUCHE

1:2-iso*Propyliden*-D-*xylose* (I).[1] 65 g 1:2-3:5-Di-*iso*propyliden-D-xylose[2] werden durch kräftiges Schütteln in 500 cm³ Wasser verteilt und nach Zugabe von 1,3 cm³ konz. HCl ($d = 1{,}18$) 3,5 Stunden geschüttelt. Nach Neutralisation mit einer gesättigten Sodalösung und nach dem Eindampfen i.V. wird der Rückstand mit Aceton

* Siehe Dr-Dissertation M. Burgdorf, Universität Bonn (1956).

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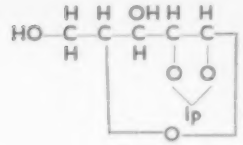
[2] P. A. Levene u. A. L. Raymond, *J. Biol. Chem.* **102**, 317 (1933).

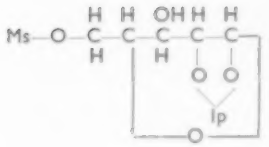
[3] S. Akiya u. T. Osawa, *J. Pharm. Soc. Japan* **76**, 1276 (1956); *Chem. Abstr.* **51**, 4284a (1957).



(I)

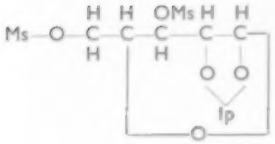
Ip = *iso*Propyliden

$>C(CH_3)_2$

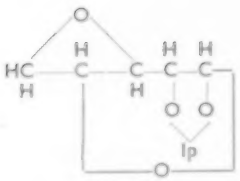


(II)

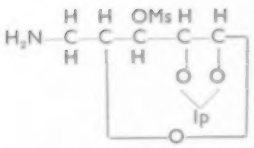
Ms = Methansulfonyl-
($H_3C—SO_2—$)



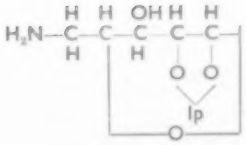
(III)



(IV)



(V)



(VI)

ausgezogen, die Acetonlösung wird i.V. eingedampft und der sirupöse Rückstand bei etwa 0,4 Torr fraktioniert destilliert. Nach einem sehr geringen Vorlauf (Ausgangsmaterial) geht die 1:2-*iso*Propyliden-D-xylose bei 140–141° über, die letzten Anteile bis etwa 150°. Das zunächst sirupöse Destillat erstarrt nach einigen Tagen im Kühlschrank kristallin. Die Ausbeute ist fast quantitativ (52,8 g). Die Substanz ist sehr hygroskopisch. Sie schmilzt zwischen 40 und 50°. Ihre Drehung in Wasser: $[\alpha]_D^{22} = -19{,}9°$ stimmt mit den Angaben der Literatur[1] überein.

1:2-iso*Propyliden*-5-*mesyl*-D-*xylose* (II). Eine Lösung von 19 g (100 mMol:) 1:2-*iso*Propyliden-D-xylose(I) in 100 cm³ abs. Pyridin wird unte Kühlung mit Eis-Kochsalz tropfenweise mit 8,5 cm³ (110 mMol) Methansulfochlorid versetzt. Nach einstündigem Aufbewahren im Kühlschrank wird die Lösung in 400 cm³ Eiswasser eingerührt, es wird fünf—sechs mal mit $CHCl_3$ ausgeschüttelt und die vereinigten Chloroformlösungen werden, nach dem Waschen mit $KHSO_4$-Lösung und mit Wasser und nach Trocknen mit Na_2SO_4, mit Petroläther bis zur bleibenden Trübung versetzt. Es scheidet sich die 1:2-*iso*Propyliden-5-mesyl-D-xylose in feinen farblosen schon sehr reinen Kristallnädelchen ab. Die Substanz schmilzt bei 129°, beim weiteren Erhitzen kristallisiert sie wieder um dann erneut bei 133° zu schmelzen. Ausbeute 19,5 g, d.i. etwa 73% d. Th., $[\alpha]_D^{20} = -0{,}68 \times 5/0{,}1607 \times 1 = -21{,}2°$ (in Methanol). ($C_9H_{16}O_7S$ (268,28). Ber. C, 40,3; H, 6,01; S, 11,95. Gef. C, 40,49; H, 6,15; S, 12,13).

1:2-iso*Propyliden*-3:5-*dimesyl*-D-*xylose* (III). Eine Lösung von 19,0 g (0,1 Mol) 1:2-*iso*Propyliden-D-xylose[1] in 120 cm³ abs. Pyridin wird unter Kühlung mit Eis-Kochsalz und unter kräftigem Rühren im Lauf von etwa Stdn. tropfenweise mit 32 ccm (= 47,5 g = 0,415 Mol) Methansulfochlorid (=Mesylchlorid) versetzt. Nach weiteren 2,5 Stunden bei etwa 0° wird die Mischung, aus der sich Pyridiniumsalze abgeschieden haben, in dünnem Strahl unter kräftigem Rühren in 750 ccm Eiswasser eingegossen. Das dabei ausfallende, häufig schon kristalline Dimesylderivat wird durch Umkristallisieren aus 250 ccm Methanol gereinigt. Ausbeute 32,5 g, d.i. 94% d. Th., $[\alpha]_D^{21} = -0{,}67° \times 5/0{,}1502 \times 1 = -22{,}3°$(in $CHCl_3$) ($C_{10}H_{18}O_9S_2$ (346,4). Ber. C, 34,67; H, 5,24; S, 18,51. Gef. C, 34,70; H, 5,28; S, 18,24).

Die Substanz ist leicht löslich in Chloroform, in heissem Wasser, Methanol und Aethanol, schwer bis unlöslich in Aether und Petroläther. Sie reduziert Fehling erst nach saurer Hydrolyse.

1:2-iso*Propyliden*-3:5-*anhydro*-D-*xylose* (IV). 29·5 g Sbst. (III) werden in einer frisch hergestellten, klarfiltrierten Lösung von 250 g KOH in 1800 cm³ abs. Alkohol 20 Stunden lang geschüttelt. Dabei geht die Dimesylverbindung allmählich in Lösung und es kristallisiert das Kalium-methansulfonat in charakteristischen feinen Nadeln aus. Die filtrierte Lösung wird unter Eiskühlung durch Einleiten von CO_2 möglichst neutralisiert, von dem dabei ausfallenden Kristallbrei wird nach Verdünnen der Mischung mit 500 ccm abs. Aethanol möglichst vollständig abfiltriert, mit abs. Alkohol gut ausgewaschen und es werden die vereinigten Filtrate i.V. eingedampft. Dabei noch manchmal sich ausscheidende weitere Salze werden ebnfalls abfiltriert. Der Verdampfungsrückstand wird mit abs. Chloroform verrieben, der klar filtrierte Chloroformauszug wird mit Na_2SO_4 getrocknet, mit Kohle geklärt, i.V. zum Sirup eingedampft und dieser fraktioniert destilliert. Bei 0,08 Torr geht die Anhydroverbindung zwischen 53 und 54° über. Das Destillat erstarrt nach kurzer Zeit im Kühlschrank kristallin. Ausbeute 12,5 g, d.i. 85% d. Th. Zusammensetzung,

Schmelzpunkt (16–17°) und Drehung [$[\alpha]_D^{25} = 14{\cdot}3°$ (in Wasser)] stimmen mit der Literatur[2] überein.

1:2-iso*Propyliden-3-mesyl-5-deoxy-5-amino-D-xylose* (V). 6 g 1:2-*iso*Propyliden-3:5-dimesyl-D-xylose(III) werden mit 75 cm³ einer bei 0° gesättigten Lösung von NH_3 in abs. Methanol im Einschlussrohr (kalt einfüllen!) 6 Stunden lang auf 100° (Wasserdampf) erhitzt. Die erkaltete, schwachgelbe Lösung hinterlässt nach dem Eindampfen einen kristallinen Rückstand, Methansulfonat (Salz) der 1:2-*iso*Propyliden-3-mesyl-5-deoxy-5-amino-D-xylose in fast quantitativer Ausbeute. In Wasser, in Methanol und Alkohol ist das Salz in der Hitze löslich. Durch Lösen in heissem Methanol und Abkühlen der mit Aether versetzten Lösung lässt es sich leicht umkristallisieren. Es schmilzt bei 201°, $[\alpha]_D^{20} = +0{,}17 \times 5/0{,}1854 \times 1 = +4{,}58°$ (in Wasser) ($C_{10}H_{21}O_9NS_2$ (363,41). Ber. C, 33,04; H, 5,82; S, 17,65; N, 3,85. Gef. C, 33,30; H, 5,81; S, 17,60; N, 3,84).

Zur Gewinnung der freien Base werden 10,0 g des Methansulfonats in 350 cm³ abs. Methanol mit einer Lösung von 1,57 g KOH in 40 cm³ abs Methanol versetzt. Es kristallisiert bald ein Teil des Kalium-methansulfonats aus. Das Filtrat wird zur Trockne verdampft und der Rückstand mehrfach mit $CHCl_3$ ausgezogen. Nach dem Verdampfen dieser Lösung hinterbleibt die Base als Sirup, der aber meist bald kristallisiert. (Reiben). Ausbeute quantitativ. Aus einer Mischung von Benzol mit Ligroin (1 zu 6) lässt sich die Verbindung umkristallisieren. Sie schmilzt dann bei 89°. Sie ist leicht löslich in Wasser und in den meisten organischen Lösungsmitteln, bis auf Ligroin und Petroläther. Die wässrige Lüsung reagiert alkalisch. Fehling wird erst nach saurer Hydrolyse reduziert. $[\alpha]_D^{25} = -0{,}22° \times 5/0{,}1225 \times 1 = -9{,}0°$ (in Methanol). ($C_9H_{17}O_6NS$ (267,30). Ber. C, 40,42; H, 6,41; N, 5,24; S, 11,99. Gef. C, 40,41; H, 6, 40; N, 5,15; S, 11,96).

1:2-iso*Propyliden-5-deoxy-5-amino-D-xylose*.[3] (VI) (*A*) Eine Lösung von 1 g 1:2-*iso*-Propyliden-5-mesyl-D-xylose(II) in 12,5 cm³ bei 0° mit NH_3 gesättigtem Methanol wird im geschlossenen Gefäss sechs Stunden lang auf 100° (siedendes Wasserbad) erhitzt. Nach dem Abkühlen, zuletzt in Eis-Kochsalz, wird die Lösung i.V. zu einem schwach gelben Sirup eingedampft. Durch Auflösen in Methanol und versetzen dieser Lösung mit Aether bis zur ersten bleibenden Trübung erhält man die 1:2-*iso*-Propyliden-5-deoxy-5-amino-D-xylose als methansulfonsaures Salz in schon recht reinen Kristallen vom Schmelzpunkt 146–147°. Ausbeute, zusammen mit einer weiteren aus der Mutterlauge durch Einengen gewonnenen Portion 0,93 g, d.i. 88 % d. Th. Die Substanz ist leicht löslich in Wasser, löslich in Methanol, schwer bis unlöslich in den sonstigen gebräuchlichen organischen Lösungsmitteln. Die Lösung in Wasser reagiert gegen Lakmus neutral. $[\alpha]_D^{20} = -0{,}34° \times 5/0{,}1985 \times 1 = -8{,}5°$ (in Wasser) ($C_9H_{19}O_7NS$ (285,32). Ber. C, 37,88; H, 6,75; N, 4,90; S, 11,21. Gef. C, 37,88; H, 6,71; N, 4,91; S, 11,24).

Das gleiche Salz kristallisiert beim Zusammengeben einer Lösung von 1:2-*iso*Propyliden-5-deoxy-5-amino-D-xylose(1 g in 25 cm³ $CHCl_3$) mit einer Lösung von 0,508 g Methansulfonsäure in 10 cm³ abs. Aether—am Besten beim Animpfen—in fast quantitativer Ausbeute aus.

(*B*) Eine, wenn nötig mit Kohle geklärte, Lösung von 5,5 g 1:2-*iso*Propyliden-3-mesyl-5-deoxy-5-amino-D-xylose(V) in 220 cm³ abs. Methanol wird mit einer Lösung vor 22 g KOH in 350 cm³ abs. Methanol 30 Stunden lang rückgekocht. Nach dem Abkühlen haben sich 1,6 g, *d.i.* etwa 3/5 der berechneten Menge Kaliummesylat

kristallin abgeschieden. Das Filtrat wird bis zur vollständigen Abscheidung von K_2CO_3 mit CO_2 gesättigt (2 Stunden), es wird vom Salz abgesaugt und das Filtrat i.V. zur Trockne verdampft. Der Rückstand wird mehrfach mit Benzol extrahiert; die vereinigten Benzollösungen werden i.V. eingedampft. Der Rückstand kristallisiert beim Anreiben. Die Substanz kann durch Versetzen der Lösung in Benzol mit Ligroin bis zur schwachen Trübung und Abkühlen der Mischung auf etwa $-20°$ weiter gereinigt werden. Sie ist leicht löslich in Wasser und Methanol, löslich in Benzol, Aceton und Chloroform, schwer in Aether, so gut wie unlöslich in Ligroin und Petroläther. Die wässrige Lösung reagiert alkalisch. Die reine Substanz schmilzt bei 92–93°. Ausbeute 3,89 g, d.i. 71% d. Th. Auch in reinem kristallinen Zustand ist die Substanz nicht sehr haltbar. Schon nah einigen Tagen beginnt sie sich unter Verfärbung zu zersetzen. $[\alpha]_D^{25} = -0{,}19 \times 5/0{,}0760 \times 1 = -12{,}5°$ (in Methanol). ($C_8H_{15}O_4N$ (189,21). Ber. C, 50,80; H, 7,99; N, 7,40. Gef. C, 50,92; H, 7,94; N, 7,15).

Tetrahedron, 1958, Vol. 3, pp. 279-302. Pergamon Press Ltd., London

LE DIPTÉROCARPOL—I

PRÉPARATION DE LA 8,14-DIMÉTHYL 18-NOR-TESTOSTÉRONE

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Résumé—Les sécrétions de 4 espèces de *Dipterocarpus* Viêt-Namiens ont fourni un triterpène tétracyclique, identifié au diptérocarpol de van Itallie et à l'hydroxy-dammarénone-II (I) de Mills. Le diptérocarpol est dégradé (chaîne latérale) et modifié (cycle A) en un analogue de la testostérone (XXX). Sa stéréochimie est discutée.

Abstract—A tetracyclic triterpene has been isolated from the oleoresins of four *Dipterocarpus* species. It has been identified with van Itallie's dipterocarpol and Mills' hydroxy-dammarenone-II (I). The side chain of dipterocarpol has been degraded to the methyl ketone (VII, R = H, by three different methods. Trifluoroperacetic acid converted the ketone into the 17-acetate (XXII, R = H, R′ = Ac), and ring A has then been modified by a classical method to a pharmacologically inactive analogue of testosterone (XXX, R = H). The stereochemistry of dipterocarpol is discussed.

La famille des *Dipterocarpaceae* comprend de nombreuses espèces arborescentes du Sud-Est asiatique, caractérisées du point de vue phytochimique par l'abondance de leurs sécrétions oléorésineuses ou résineuses. Certaines de ces sécrétions ont, ou ont eu, une certaine importance économique: bornéol de *Dryobalanops*, résines Dammar de *Hopea* et *Shorea*, baumes de gurjun de *Dipterocarpus*.[1]

Nous devons à Messieurs L. Cosserat, P. Maurand puis Luong-Si Chuong‡ des échantillons de baumes de gurjun provenant d'arbres bien identifiés: *Dipterocarpus Dyeri*, *D. alatus*, *D. intricatus* et *D. artocarpifolius*. Ces baumes se présentent sous forme d'huiles visqueuses laissant peu à peu précipiter un sédiment solide incolore aisément isolable. Le travail dont nous rendons compte ici est consacré d'une part à l'identification du constituant principal de ce *sédiment solide*, le diptérocarpol, et d'autre part à son utilisation pour une synthèse d'un analogue de la testostérone. L'étude de la fraction *liquide* est actuellement en cours.

ISOLEMENT ET CARACTÉRISATION DU DIPTÉROCARPOL

Le sédiment solide des quatre espèces de *Dipterocarpus* étudiées comprend une petite quantité de produits amorphes peu solubles ('résènes' polymérisés; cf. l'emploi local du baume de gurjun comme huile siccative), et un constituant cristallin quasi-exclusif, aisément purifié par cristallisation.

Les constantes physiques de ce produit, sa composition et son origine, ne laissent aucun doute sur son identité avec le "diptérocapol" isolé par van Itallie d'une

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‡ Notre attention a initialement été attirée sur l'intérêt des sécrétions de *Dipterocarpus* par Monsieur L. Cosserat, Chef de Travaux à la Faculté des Sciences de Saïgon, qui a participé aux premiers travaux d'isolement. Nous lui exprimons ici toute notre reconnaissance, ainsi qu'à Messieurs P. Maurand et Luong-Si Chuong, Chefs du Service des Recherches Forestières du Viêt-Nam, qui nous ont obligeamment procuré les échantillons utilisés dans ce travail.

[1] A. Tschirch et E. Stock, *Die Harze* (3ème Ed.) Vol. II, pp. 388–467. Borntraeger, Berlin (1935).

sécrétion de *Dipterocarpus Hasseltii* (ou *trinervis*).[2] Cette identification est confirmée par les constantes physiques et la composition d'une trinor-lactone (II) déjà obtenue par van Itallie (Tableau 1). La masse moléculaire a été aimablement déterminée par Monsieur D. Rogers (Cardiff) par radiocristallographie: 438 ($C_{30}H_{50}O_2$ = 442,70) [cryoscopie dans le benzène: 433[2a]].

TABLEAU 1

	Diptérocarpol (Réf. 2)	Produit de *Dipterocarpus* (cf. Partie Exp.)
Point de fusion	134–135°	135–136°
Pouvoir rotatoire	$[\alpha]_D$ + 64,6° (Chf)	$[\alpha]_D$ + 65° (Chf)
Formule brute	"$C_{27}H_{46}O_2$"	$C_{30}H_{50}O_2$
	Trinor-lactone (II)	
Point de fusion	183–184°	183°
Pouvoir rotatoire	$[\alpha]_D$ + 71° (Chf)	$[\alpha]_D$ + 69° (Chf)
Formule brute	"$C_{27}H_{44}O_3$"	$C_{27}H_{42}O_3$

I

II

Une analyse fonctionnelle classique montre la présence dans le diptérocarpol d'une fonction *cétone* dans un cycle à six chaînons au moins ou dans une chaîne, d'une *double-liaison* trisubstituée et d'un *hydroxyle* tertiaire. Il en résulte pour le squelette carboné un système *tétracyclique*, suggérant évidemment la nature *triterpénique* du produit. Une étude préliminaire ne nous avait pas permis de déterminer la structure du diptérocarpol, mais nous avait du moins amenés à retenir une hypothèse de travail raisonnable, (I); nous ne décrirons pas séparément cette étude dont la plus grande partie est utilisée par la suite, la formule (I) ayant été effectivement prouvée par Mills[3] comme étant celle de l'un des constituants des résines Dammar commerciales, l'"hydroxy-dammarénone-II".* Une comparaison directe avec des échantillons de ce produit et de sa trinor-lactone de coupure (II), aimablement fournis par Monsieur J. S. Mills, a confirmé cette identification.

Enfin, presque simultanément, le diptérocarpol a aussi été retrouvé par Godson

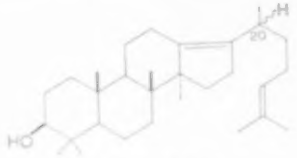
* Les résines Dammar contiennent notamment, en plus de constituants acides et de produits pentacycliques, les dérivés 3β-hydroxylés et 3-cétoniques des séries 20α- et 20β-hydroxylées (séries dites "I" et "II") et de la série 20(21)-éthylénique, correspondant au squelette (I). Ces corps, isolés par Mills et Werner de résines Dammar commerciales, ont été retrouvés par Monsieur J. S. Mills par chromatographie sur papier, dans des échantillons de Dammar de *Hopea odorata* et *Shorea vulgaris* que nous avait fournis Monsieur P. Maurand; leur composition est très voisine de celle des échantillons commerciaux.

[2] L. van Itallie, *Arch. Pharm.* **250**, 204 (1912).
[2a] J. S. Mills et A. E. A. Werner, *J. Chem. Soc.* 3132 (1955); [b] J. S. Mills, *Ibid.* 2196 (1956).

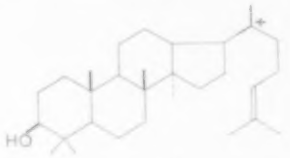
et al.[4] dans le *bois* de *Dipterocarpus Lowii* et de deux autres *Dipterocarpus* non identifiés.

Le diptérocarpol est donc un constituant commun de nombreuses espèces de *Dipterocarpaceae*; son isolement est évidemment facilité quand il se sépare spontanément à l'état presque pur, comme dans les espèces de *Dipterocarpus* que nous avons étudiées.

Sa structure, bâtie sur le même squelette que celles de l'*iso*euphol (A) et de l'*iso*tirucallol (B), présente un intérêt exceptionnel du fait que l'ion carbonium correspondant en C-20 (C)† avait été explicitement postulé par Ruzicka[5a] comme le premier intermédiaire tétracyclique dans la biogénèse de l'euphol et de nombreux autres triterpènes tétra- et pentacycliques, à partir du squalène. C'était d'ailleurs une des raisons qui nous avaient fait retenir l'hypothèse de travail (I).



A: 20βH B: 20αH



C

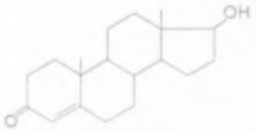
La facilité d'obtention de quantités assez importantes de diptérocarpol nous a alors permis d'envisager son utilisation pour la préparation d'analogues d'hormones stéroïdes[6], ayant le *même* squelette tétracyclique et la *même* stéréochimie (voir plus bas), mais dont les hydrogènes angulaires en 8 et 14 seraient remplacés par des groupes méthyles, et le groupe méthyle en 13 (C-18) par un hydrogène. Nous décrivons ici la préparation, en une quinzaine d'étapes à partir du diptérocarpol, de l'analogue (XXX, R = H) de la testostérone (D). Cette préparation exige:

(i) la dégradation de la chaîne latérale du diptérocarpol

(ii) la modification du cycle A.

Les méthodes utilisées pour ces transformations suivent des voies pour la plupart déjà explorées dans d'autres séries.

XXX



D

Dégradations de la chaîne latérale du diptérocarpol

Le projet que nous avons retenu utilise, comme point de départ pour des dégradations plus profondes, la méthyl-cétone (VII, R = H), déjà décrite par Mills.[3b] Ce dernier l'avait obtenue, comme le montre le Tableau 2, en mélange environ 1:1 avec la 21-nor 20-cétone (VIII). La séparation des acétates de ces deux cétones exige une

† Numérotage correspondant à la nomenclature systématique utilisée dans la partie expérimentale.

[4] D. H. Godson, F. E. King et T. J. King, *Chem. & Ind.* 190 (1956).

[5a] L. Ruzicka, *Experientia* **9**, 357 (1953); [b] A. Eschenmoser, L. Ruzicka, O. Jeger et D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955).

[6] On trouvera des listes des modifications apportées aux hormones stéroïdes dans *Ann. Rep.* **52**, 209 (1955); *Ibid.* **53**, 223 (1956).

chromatographie soignée, et ni Mills ni nous-mêmes n'avons pu la réaliser complètement sur 100 fois le poids d'alumine. Nous avons donc essayé d'obtenir des quantités suffisantes de la méthyl-cétone (VII) pure par deux autres voies: l'une facilitant la séparation des deux produits cétoniques formés, l'autre assurant la formation exclusive du produit désiré.

Dans la première de ces voies (Tableau 2), la trinor-lactone (II) est réduite par

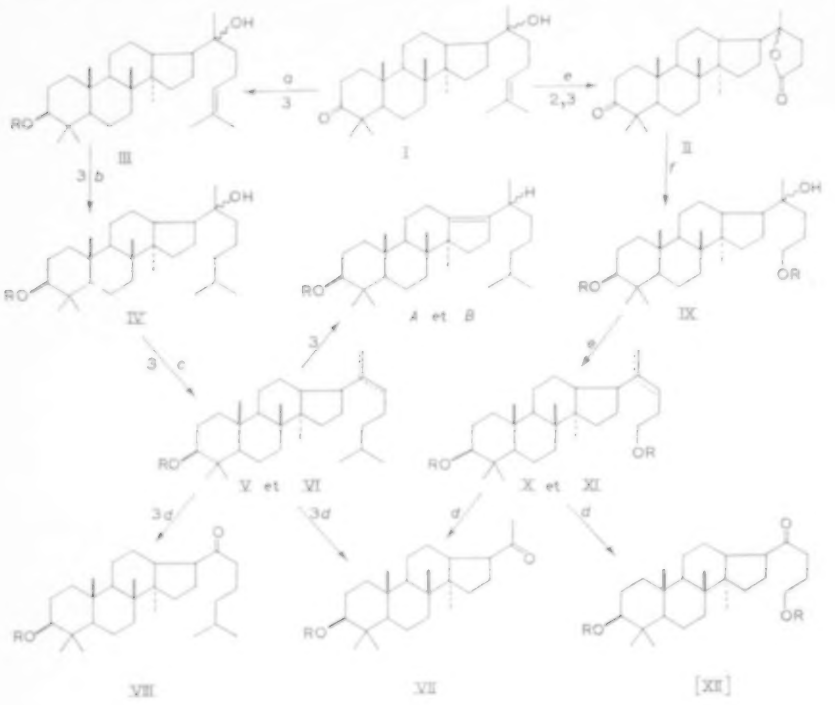


TABLEAU 2. RÉACTIFS UTILISÉS

a: BH_4K, Di, H_2O	*d*: O_3, AcOH
b: H_2, Pd, Di	*e*: CrO_3, AcOH
c: $POCl_3$, Py, Bz	*f*: $LiAlH_4$, THF

l'hydrure de lithium et d'aluminium en 3β,20ξ_2,24-triol (IX, R = H). Le 3,24-diacétate de ce triol (IX, R = Ac) est déshydraté par l'oxychlorure de phosphore et la pyridine, et le mélange d'oléfines (X + XI, R = Ac) est ozonisé pour donner la méthyl-cétone (VII, R = Ac), et la 20-cétone (XII, R = Ac) qui, en tant que *di*acétate, est facilement éliminée par chromatographie parce que plus fortement adsorbée. Le rendement en méthyl-cétone (VII) est cependant très peu satisfaisant.

La dernière voie de dégradation de la chaîne latérale (Tableau 3) fait appel à la trinor-lactone (XIII, R = Ac)[3a] qui est dégradée comme une lactone analogue obtenue comme sous-produit de l'oxydation chromique du 5,6-dibromure de l'acétate de

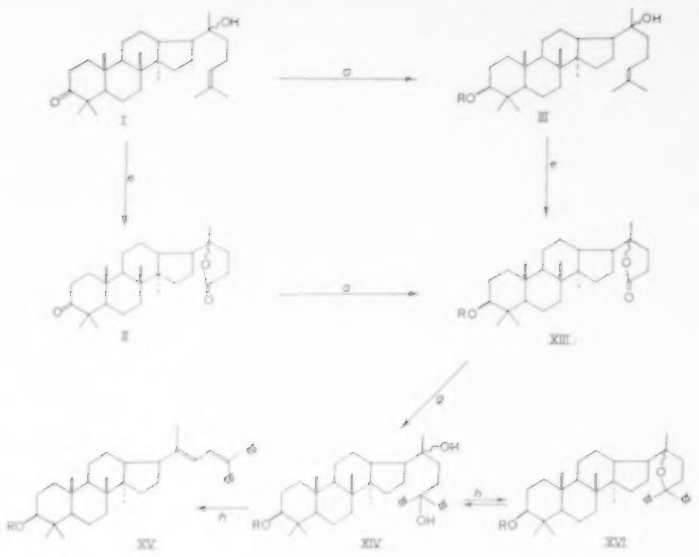


TABLEAU 3. RÉACTIFS UTILISÉS

a:	BH_4K, Di, H_2O	*g*:	C_6H_5MgBr, Et_2O, Bz
e:	CrO_3, AcOH	*h*:	p.TsOH, AcOH

cholestérol.[7] Le bromure de phényl-magnésium conduit au triol (XIV, R = H). Le 3-acétate correspondant (XIV, R = Ac) est déshydraté en milieu acide pour donner le dérivé diphényl-butadiénique (XV, R = Ac), dont l'oxydation chromique donne la méthyl-cétone (VII). L'étape critique est ici la déshydratation. Un premier essai encourageant avec l'acide oxalique ne put ensuite être reproduit. Un excellent rendement est par contre obtenu avec l'acide *p*-toluène-sulfonique dans l'acide acétique, à 80°, en suivant au spectrophotomètre le développement de la bande d'absorption du chromophore diphényl-butadiénique.

Les acides faibles conduisent de préférence à la déshydratation du diol (XIV, R = Ac) en dérivé tétrahydrofurannique (XVI, R = Ac)[7d]. Cette déshydratation est extraordinairement aisée: elle est par exemple quantitative, en quelques minutes à 20°, par action de bichromate de sodium dans l'acide acétique, sur une solution du diol (essai de formation d'un ester chromique![8]). Le dérivé tétrahydrofurannique est

[7] [a] K. Miescher et W. H. Fischer, *Helv. Chim. Acta* **22**, 155 (1939); W. L. C. Veer et St. Goldschmidt, *Rec. Trav. Chim.* **66**, 75 (1947); [b] J. R. Billeter et K. Miescher, *Helv. Chim. Acta* **30**, 1409 (1947); cf. aussi: G. I. Kiprianov et L. N. Volobelski, *Ukrain. khim. zh.* **20**, 664 (1954); T. A. Favorskaia et N. P. Rbiova, *Zh. obshch. khim.* **26**, 423 (1956).

[8] L. F. Fieser et G. Ourisson, *Bull. Soc. Chim. Fr.* 1152 (1953).

aussi toujours obtenu comme sous-produit de la déshydratation par l'acide *p*-toluènesulfonique; il peut être transformé lentement par ce réactif en dérivé diphényl-butadiénique.

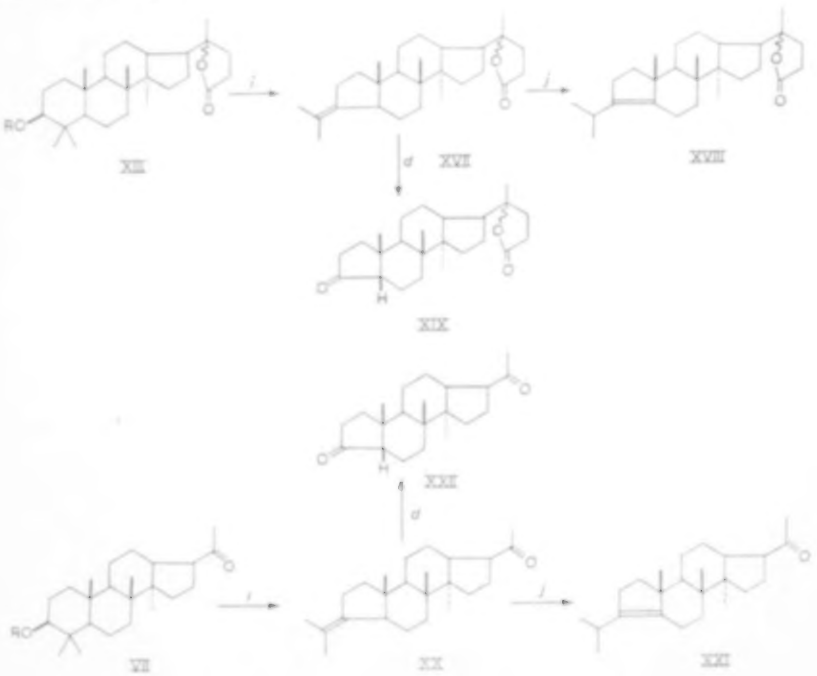
La dégradation de la chaîne latérale du diptérocarpol est complétée par coupure de la méthyl-cétone par l'acide trifluoroperacétique en présence de phosphate disodique.[9] Le milieu est suffisamment peu acide pour permettre d'effectuer la réaction, avec un excellent rendement, sur la 3-*hydroxy* méthyl-cétone (VII, R = H; Tableau 4).

TABLEAU 4. RÉACTIFS UTILISÉS

d: O_2, AcOH *i*: PCl_5, Bz *j*: ClH, Chf

Le 3-hydroxy 17-acétate (XXIII, R = H, R' = Ac) ainsi obtenu est directement utilisable pour les modifications prévues du cycle A, une protection de la fonction en 17 étant automatiquement réalisée. Pas plus qu'en série stéroïde avec l'acide perbenzoïque,[10] nous n'avons observé d'attaque en 21 sur la méthyl-cétone; mais il faut insister sur la rapidité de la réaction avec l'acide trifluoroperacétique, alors que l'acide perbenzoïque exige plusieurs jours à 30° pour donner le même résultat.

Modifications du cycle A



Nous décrivons dans la Partie Expérimentale, et avons résumées dans le Tableau 4, quelques réactions-pilotes effectuées sur le cycle A de la lactone (XIII) et de la méthyl-cétone (VII) avant leur utilisation avec l'acétate (XXII), décrite dans le Tableau 5.

[9] W. D. Emmons et A. S. Pagano, *J. Amer. Chem. Soc.* **77**, 2287 (1955); W. F. Sager et A. Duckworth, *J. Amer. Chem. Soc.* **77**, 188 (1955).
[10] L. H. Sarett, *J. Amer. Chem. Soc.* **69**, 2899 (1947).

Pour éliminer le groupe *gem*-diméthyle en 4, et introduire le systéme 3-cétone α,β-éthylénique caractéristique des hormones stéroïdes, nous avons suivi la méthode

TABLEAU 5. RÉACTIFS UTILISÉS

d:	O_3, AcOH	*l*:	CH_3MgI, Bz
i:	PCl_5, Bz	*m*:	OsO_4, Py; $LiAlH_4$, Et_2O
j:	ClH, Chf	*n*:	$Pb(OAc)_4$, AcOH
k:	CF_3CO_3H, CH_2Cl_2	*o*:	KOH, EtOH

décrite par l'Ecole de Zürich,[11] et aussi utilisée par Barton *et al.*,[12] dans la série du lanostérol.

Le dérivé isopropylidénique (XXIV, R = Ac), obtenu par action du pentachlorure de phosphore dans le benzène, avec *barbotage* d'azote[13] donne par ozonisation la A-*nor* 3-cétone (XXV, R = Ac). L'iodure de méthyl-magnésium dans le benzène* conduit, après acétylation, au méthyl-carbinol (XXVI, R = Ac). La déshydratation de ce dernier, en dérivé 3(5)-éthylénique (XXVII, R = Ac), suivie par polarimétrie, est rapide et quantitative par action de gaz chlorhydrique sur une solution chloroformique de l'alcool tertiaire. Cette méthode est certainement préférable au chauffage avec de la terre à foulon activée, précédemment utilisé;[11,12] elle est comparable à une autre déshydratation globalement *cis*, celle des dérivés 14β-hydroxylés en 8(14)-ènes par l'acide chlorhydrique à froid.[14]† Le dérivé 3α-chloré, intermédiaire probable de cette déshydratation, n'a pas été isolé.

Le composé 3(5)-éthylénique (XXVII, R = Ac) est ensuite osmylé, et réduit par l'hydrure de lithium et d'aluminium[13] en triol (XXVIII, R = H). La coupure de ce triol par le tétracétate de plomb donne la dicétone (XXIX), non isolée, dont la cétolisation en milieu alcalin est spontanément suivie de déshydratation. En contrôlant la réaction spectrophotométriquement, on obtient ainsi la 8,14-*diméthyl* 18-*nor*-*testostérone* (XXX) désirée.

Essais pharmacologiques

Des essais pharmacologiques ont été aimablement effectués sous la direction du Dr. Overbeek (N. V. Organon, Oss, Hollande). Alors que le dérivé du lanostérol (E) possède, d'après Barnes[15] une activité progestative notable, son analogue de la série du diptérocarpol (VII, R = H), qui n'en diffère que par l'*échange* d'un groupe méthyle et d'un hydrogène de 13 en 8, et inversement, s'est révélé inactif dans le test de clauberg De même, l'analogue (XXX, R = H) de la testostérone n'a manifesté aucune activité androgénique ni anabolique, dans le test de Herschberger. Cette observation est assez inattendue, par suite de l'activité observée dans d'autres analogues de la testostérone, modifiés par perte ou gain de groupes méthyles, angulaires ou non.[6] Une "explication" simple de cette inactivité serait que la stéréochimie du produit final ne corresponde *pas* à celle de la testostérone. Nous devons donc discuter cette possibilité.

* Avec l'iodure de méthyl-magnésium dans l'éther ou le méthyl-lithium dans le tétrahydrofuranne, aucune réaction n'a eu lieu, sans doute par suite des exigences stériques plus grandes des réactifs solvatés.

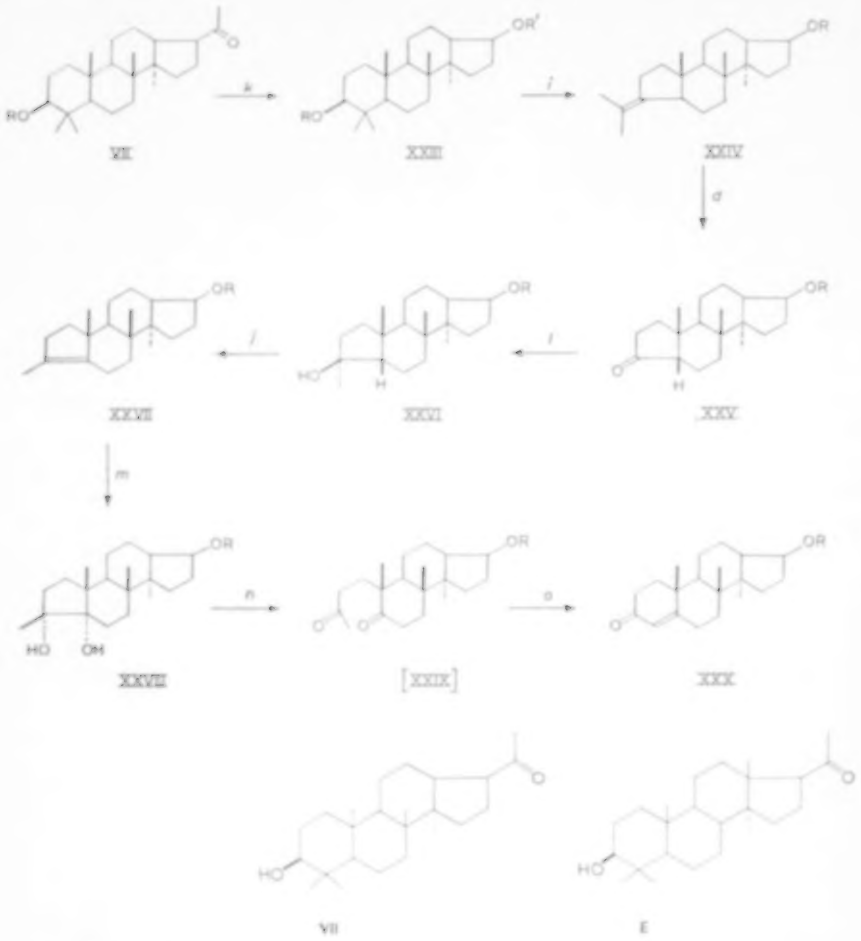
† Nous remercions Monsieur O. Schindler (Bâle) d'avoir attiré notre attention sur cette analogie.

[11a] W. Voser, D. E. White, H. Heusser, O. Jeger et L. Ruzicka, *Helv. Chim. Acta* **35**, 830 (1952); [b] W. Voser, H. Heusser, O. Jeger et L. Ruzicka, *Ibid.* **36**, 299 (1953).

[12] D. H. R. Barton, D. A. J. Ives et B. R. Thomas, *J. Chem. Soc.* 903 (1954).

[13] J. B. Barbour, W. A. Lourens, F. L. Warren et K. H. Watling, *J. Chem. Soc.* 2194 (1956).

[14] S. Smith, *J. Chem. Soc.* 354 (1936); H. M. E. Cardwell et S. Smith, *Ibid.* 2012 (1954).



VII XXII XXIV XXVII XXVI XXV XXVIII [XXIX] XXX

VII E

Aspects stéréochimiques

La stéréochimie de notre analogue de la testostérone est nécessairement la *même* que celle du diptérocarpol en 8, 9, 10, 13 et 14, positions dont la configuration n'a pu être affectée à aucune étape. En 8, 9, 10 et 14, cette stéréochimie est définie (8β, 9α, 10β, 14α) par la conversion du diptérocarpol en *iso*euphénol et *iso*tirucallénol par Mills[2d] (*Cf.* Tableau 1).

La configuration de C-13 est liée à celle de C-17 comme nous le montrerons maintenant.

L'orientation du groupe –OH en 17 est la même que celle du groupe $-CO-CH_3$ en 17 de la méthyl-cétone (VII), et que celle du groupe $-CO-C_6H_{13}$ de la 20-cétone (VIII) qui nous a aussi conduits au même dérivé 3β,17-dihydroxy (XXII, R = R′ = H); en effet, la coupure des cétones par les peracides se fait avec rétention de configuration.[16*]

* En toute rigueur, ceci n'est assuré que si la cétone traitée n'est pas épimérisée *avant* la coupure. Ici, le milieu est peu acide, et les cétones de départ sont les épimères *stables*.

[15] C. S. Barnes, *Austr. J. Chem.* **9**, 228 (1956).

[16] R. B. Turner, *J. Amer. Chem. Soc.* **72**, 878 (1950).

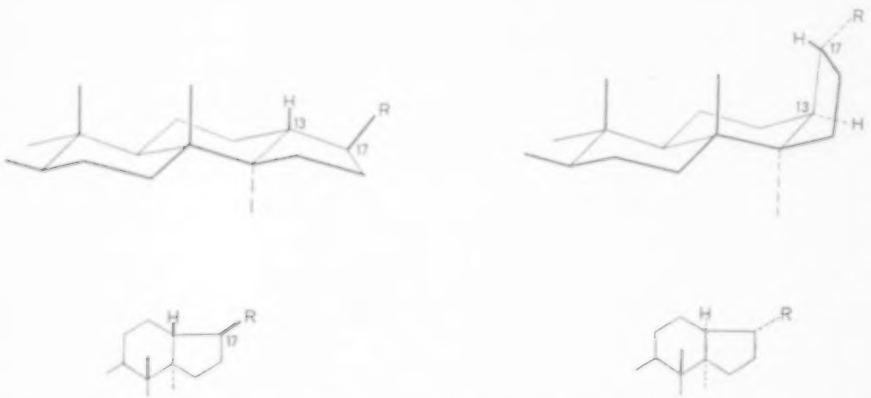
La configuration en 17 de la méthyl-cétone (VII) et de la nor-cétone (VIII) est par ailleurs:

d'une part la configuration *stable* (ceci avait déjà été montré par Mills)

d'autre part *la même* que celle du diptérocarpol; par action de l'iodure de méthyl-magnésium sur la nor-cétone (VIII), nous avons en effet obtenu un mélange d'alcools tertiaires, duquel nous avons pu isoler pur le composé (IV), déjà obtenu à partir du diptérocarpol:

VIII IV

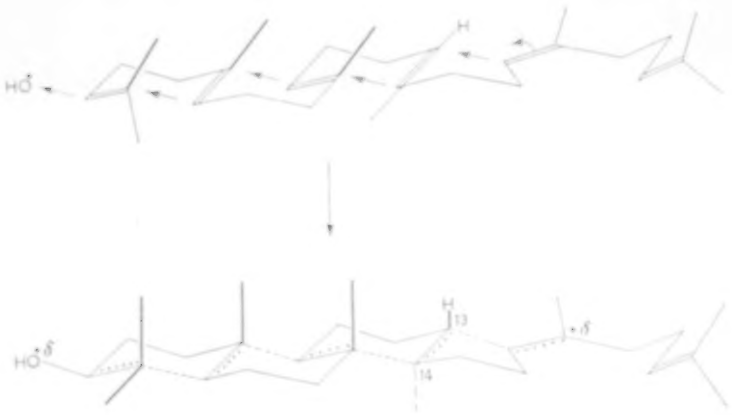
Une étude de modèles moléculaires confirme l'impression se dégageant des représentations graphiques conventionnelles: *deux* arrangements stéréochimiques en 13 et 17 sont compatibles avec ces données: (F), qui correspond à la stéréochimie de la testostérone (13β, 17α H) et (G), qui en est épimère en 13 *et* 17.



Nous espérons présenter plus tard les éléments d'une décision définitive entre ces deux possibilités; un argument rend cependant dès maintenant seule probable la structure (F), dont la stéréochimie est "correcte."

En effet, l'orientation 13βH est une conséquence *nécessaire* du mécanisme hypothétique de biogénèse proposé par Eschenmoser *et al.*,[5b] dont toutes les conséquence et toutes les prédictions ont jusqu'ici été vérifiées par l'expérience. La cyclisation par addition anti-parallèle sur les doubles-liaisons d'un squalène tout-*trans*, replié en une succession de quasi-cycles, implique une orientation relative *trans* des groupes angulaires en 14 (α-CH_3) et 13 (donc β-H). Cette orientation ne dépend pas (contrairement à la configuration en 17) de la *conformation* du quasi-cycle D lors de la cyclisation, mais uniquement de la nature, supposée tout-*trans*, du squalène admis comme précurseur. Le rôle du squalène tout-*trans* n'a toutefois pas encore été démontré pour la biosynthèse des triterpènes, mais seulement pour celle des stéroïdes, par l'intermédiaire du lanostérol.

Des deux arrangements, (F) et (G), chimiquement valables pour le diptérocarpol et pour notre analogue de la testostérone, seul le premier semble donc conciliable avec les hypothèses biogénétiques. Si cette conclusion est confirmée par la suite, et nous nous employons actuellement à la vérifier, l'inactivité physiologique des dérivés du diptérocarpol constituera un problème en soi, dont la discussion est prématurée.



Ce travail a bénéficié d'une généreuse subvention de N.V. Organon (Oss, Hollande), dont nous remercions ici la Direction. Nous remercions aussi pour des discussions et des suggestions utiles MM. C. Djerassi (Detroit), R. Dulou (Paris), W. Klyne (Londres), O. Schindler (Bâle), St. Szpilfogel et D. A. van Dorp (Oss).

PARTIE EXPÉRIMENTALE

Les microanalyses ont été effectuées au Laboratoire de Microanalyse de l'Ecole Normale Supérieure, sauf celles indiquées L.L., dues au Laboratoire de Microanalyse de la Faculté des Sciences de Lyon.

Les rotations ont été mesurées à 18–22° avec un tube de 1 dm, pour la raie jaune du mercure (5791 Å); elles sont arrondies au degré le plus proche, et sont considérées comme précises à $\pm$2–3° pour une concentration *c* env. = 1.

Les points de fusion ont été mesurés dans un capillaire de verre ordinaire, sauf ceux marqués (Kof.), appréciés au banc chauffant Kofler.

Les spectres I.R. ont été obtenus avec un spectrophotomètre Perkin–Elmer 21, grâce à l'obligeance de Monsieur Kopff (C.R.M., Strasbourg). *Tous* les composés purs obtenus ont été examinés en I.R.; les bandes fonctionnelles sont toutes en accord avec les structures indiquées, et ne sont indiquées ici que dans quelques cas importants.

Les spectres U.V. ont été déterminés avec un spectrophotomètre Unicam S.P. 500. (EtOH = Ethanol à 95%; CH = *cyclo*hexane).

Nous remercions Monsieur R. Lichtenberger, Directeur du Centre de Recherches de la Société d'Électrochimie, d'Électrométallurgie et des Usines Électriques d'Ugine.

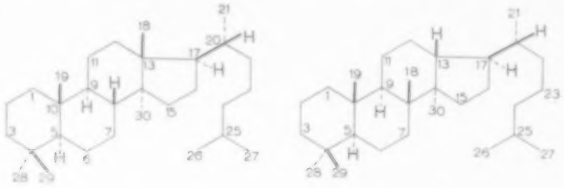
qui nous a aimablement procuré l'acide trifluoracétique et le peroxyde d'hydrogène à 85% utilisés.

Espèces étudiées. Dipterocarpus alatus Roxb, D. artocarpifolius Pierre, D. intricatus Dyer, et *D. Dyeri Pierre*. Ces identifications ont été indiquées par le Service des Recherches Forestières du Viêt-Nam, et confirmées à Strasbourg, pour *D. Dyeri*, sur échantillons de feuille, fruit et bois.

Origine des produits. Lieu de récolte: Station Expérimentale Forestière de Trang Bom (Viêt Nam). Méthode: bénitier de hauteur 30 cm, largeur 25 cm, profondeur 20 cm, sans brûlage.* Dates de récolte: 26 Février 1955 au 8 Mars 1955, et 6 au 10 Août 1956. Dimension des arbres: circonférence à 1,30 m du sol: 2 à 3 mètres.

Remarque sur la nomenclature utilisée.

Une nomenclature systématique des dérivés du diptérocarpol pourrait utiliser comme squelette fondamental le *lanostane* (H), et le modifier en 8β-méthyl-18-nor (17αH?) lanostane pour représenter (I) dont dérivent tous les composés décrits



H I

ci-dessous. C'est le système utilisé dans la Table de Pouvoir Rotatoire Naturel des Triterpènes, en préparation.[17] Pour des raisons de commodité, nous utiliserons le système proposé par Mills,[3b] en nommant "dammarane" le squelette (I), avec la numérotation indiquée ici. La configuration en 20 est inconnue; nous désignons par 20ξ_2 celle des dérivés du diptérocarpol de la série dite II par Mills.

Isolement du diptérocarpol. A partir de l'oléorésine de *Dipterocarpus Dyeri*, une filtration sous vide est assez facile; à partir des autres oléorésines, elle ne peut être effectuée que par petites fractions, en renouvelant souvent le filtre. L'essorage par centrifugation est à prohiber, car le brassage d'air active la polymérisation de la fraction sesquiterpénique et colmate l'élément filtrant. Par contre il est commode de ne soumettre à la filtration que des culots concentrés par centrifugation de l'oléorésine. Le résidu de filtration est lavé sur filtre à la ligroïne ou à l'hexane. On le dissout dans le benzène, ce qui élimine les corps étrangers (fragments de bois, insectes nombreux: fourmis, petites abeilles) et une petite quantité de polymères (résènes?). On filtre sur alumine, éventuellement après traitement par une petite quantité de charbon actif, et le produit obtenu est recristallisé dans le méthanol ou l'éthanol. Le point de fusion des premiers cristaux obtenus (129,5–131°) peut être élevé jusqu'à 136° en deux recristallisations dans l'éthanol ou l'acétate d'éthyle.

Par triangulation systématique (éthanol ou acétate d'éthyle), ou par chromatographie soignée sur alumine (40–50 fois le poids de produit), on n'a pu obtenir aucune séparation; seul le diptérocarpol a été isolé.

* Dans la pratique locale, un brûlage est généralement utilisé pour activer la sécrétion; un échantillon obtenu avec brûlage a été étudié: le diptérocarpol en a été isolé sans difficultés supplémentaires.

[17] Cf. pour les règles utilisées dans cette Table: S. Allard et G. Ourisson, *Tetrahedron*, **1**, 277 (1957).

Diptérocarpol(20 ξ_2-*hydroxy* 3-*oxo dammara*-23-*ène*) (I):

$F = 127°$, se resolidifie, puis $F = 135$–$136°$, pas de dépression avec un échantillon d'hydroxy-dammarénone-II fourni par M. J. S. Mills;

$[\alpha]_f$ $+65°$ ($c = 3{,}7$; Chf); $[\alpha]_c$ $+87°$; $[\alpha]_{indigo}$ $+152°$

$C_{30}H_{50}O_2$ (442,70)	Calc.%	C:	81,39	H:	11,38	O: 7,23
	Trouvé	C:	81,38	H:	11,40	O: 7,43
			81,41		11,36	

Spectre U.V. λ_{max}^{EtOH} 290 mμ ($\varepsilon = 32$)

Spectre I.R. ν(OH) 3620 cm^{-1} ν(C=O) 1695 cm^{-1}

$\delta(CH_2)$ 1420 cm^{-1} [$-CH_2-CO-$] doublet 1370 cm^{-1} [CMe_2]

δ(CH) 815 cm^{-1} $-CH=C<$ (C)(C)

Réaction avec le brome: décoloration immédiate avec dégagement de BrH.
Test au tétranitrométhane: jaune foncé.

2-4-*Dinitrophénylhydrazone*. Formée très facilement sous forme de gel, filtré et lavé à EtOH. Par refroidissement de la solution dans EtOH chaud, formation d'un précipité gélatineux.

Après chromatographie sur alumine neutre Woelm, le produit élué au benzène donne encore des gels. Il est lavé sur filtre à l'éthanol, et séché sous vide.

$F = 162°$ (Kof; déc.)

$C_{36}H_{54}O_5N_4$(622,82):	Calc.%	N:	9,00
	Trouvé	N:	9,29

Semicarbazone. Formée très facilement; recristallisée dans Chf–EtOH. Aiguilles incolores,

$F = 206$–$207°$ (Kof).

$C_{31}H_{53}O_3N_3$ (501, 75):	Calc.%	C:	74,50	H:	10,69	N: 8.41
	Trouvé	C:	74,34	H:	10,75	N: 8,41
		C:	74,64	H:	10,80	

Oximation. (dosage): 1 carbonyle.

Microhydrogénation.

Pd 5% sur CO_3Ca,	EtOH à 95%:	1 H_2 absorbé.
Pt d'Adams,	AcOH:	2 H_2 absorbés.

Essais d'acétylation

A froid, le mélange Ac_2O-Py est sans action.

Après ébullition de 18 heures, on isole un produit qui est filtré sur alumine (éther de pétrole) et cristallisé dans MeOH. Deux fractions sont obtenues.

La fraction la plus soluble donne difficilement des cristaux $F = 70$–$71°$ identifiés par point de fusion mélangé à la "dammadiènone" naturelle de Mills; c'est le 3-oxo dammara-20,24-diène.*

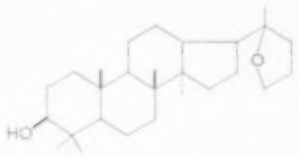
* Cf. l'"anhydro-diptérocarpol" de van Itallie,[2] obtenu par Ac_2O–AcONa: $F = 69$–$70°$; C: 84,74; 84,20; H: 11,82; 11,36%.

La fraction la moins soluble donne facilement des cristaux $F = 96°$ (Kof.) qui correspondent aussi à un produit déshydraté.

$C_{30}H_{48}O$ (424,68)	Calc.%	C:	84,84	H:	11,39
	Trouvé	C:	84,80	H:	11,24

Microhydrogénation (Pd sur CO_3Ca, AcOEt) $2H_2$ absorbés. C'est sans doute le 3-oxo dammara-20(22),24-diène.

Les spectres I.R. des produits $F = 71°$ et $F = 96°$ ne présentent pas de bande



ν(OH) ni d'autre bande ν(C=O) que celle (1695 cm^{-1}) du produit de départ. Le produit $F = 71°$ présente une bande (peu nette) ν(C=C) vers 1640 cm^{-1}.

Oxydation du diptérocarpol par l'acide chromique.

Nous avons suivi un mode opératoire identique à celui de Mills et Werner,[3] et isolé comme eux la cétone-lactone $C_{27}H_{42}O_3$ (II).

$F = 183°$. Point de fusion mélangé avec l'échantillon de Mills: pas de dépression.

Réduction de la trinor-lactone (II) *par l'hydrure de lithium et d'aluminium*

On dissout, dans 500 ml de tétrahydrofuranne distillé sur hydrure de calcium, 40 g de cétone-lactone (II); on ajoute progressivement 14 g d'hydrure de lithium et d'aluminium solide (0°; agitation). On porte une heure à reflux et on décompose l'excès de réactif par 20 ml d'acétate d'éthyle, puis 20 ml de méthanol. On dilue largement à l'eau et on évapore sous vide environ 300 ml de solvant. On filtre le précipité, et le lave, sans acidifier, avec un mélange de benzène et de chloroforme. La fraction extraite donne, par concentration, 20 g de produit cristallisé. Les eaux-mères donnent en plus 18 g d'huile jaunâtre qui n'a pu être purifiée; la présence du composé (J) y semble probable.

La fraction cristalline est recristallisée dans MeOH–H_2O; c'est le $3\beta,20\xi_2$, 24-*trihydroxydammarane* (IX, R = H): $F = 217$–$219°$ (Kof); $[\alpha]_j$ $+23°$ ($c = 1$, Di)

$C_{27}H_{48}O_3$ (420,65):	Calc.%	C:	77,09	H:	11,50
	Trouvé	C:	76,63; 77,39	H:	11,42; 11,75

Acétylation. Par acétylation (Ac_2O–Py; température ordinaire), on obtient quantitativement le 3,24-diacétate (IX, R = Ac), recristallisé dans CH_2Cl_2–Ether de pétrole:

$F = 124$–$127°$; $[\alpha]_j$ $+32°$ ($c = 1$; Chf)

$C_{31}H_{52}O_5$ (504,73):	Calc.%	C:	73,76	H:	10,39
	Trouvé	C:	73,88	H:	10,46;

2 AcO—par saponification.

Déshydratation du diacétate (IX, R = Ac) *et ozonisation des oléfines* (X *et* IX)

On traite à 20° 800 mg du diacétate (IX, R = Ac) par 20 ml de pyridine et 3 ml d'oxychlorure de phosphore. Après 1 heure, on verse avec précaution sur un mélange de glace et d'eau. On isole 780 mg de produit huileux, qui est filtré sur alumine (10 g). On élue au benzène 670 mg de fraction incolore cristallisant difficilement en présence de méthanol: $F = 119$–$124°$; $[\alpha]_i + 26°$ ($c = 1$; Chf); test au tétranitrométhane fortement positif. Ce mélange des oléfines (X et IX, R = Ac) est dissous dans 50 ml d'acide acétique et ozonisé à température ordinaire jusqu'à test négatif au tétranitrométhane. On ajoute un excès d'eau et on porte 30 min à 80°; on isole ainsi un produit huileux (680 mg) qui est chromatographié sur 15 g d'alumine. On élue (éther de pétrole-benzène 4:1) 110 mg de méthyl-cétone (VII, R = Ac), identifiée par comparaison avec un échantillon authentique obtenu par la méthode de Mills.[5b] Le rendement en méthyl cétone a pu être porté à 40% environ au plus dans différents essais. En aucun cas les fractions éluées après la méthyl-cétone n'ont fourni de produits identifiables.

Dans un essai, un entraînement à la vapeur d'eau a été effectué sur le produit d'ozonisation, et le formaldéhyde a été caractérisé dans la fraction volatile par sa 2,4-dinitrophényl-hydrazone, $F = 165°$ seule ou en mélange.

Réduction de la trinorlactone (II) *par le borohydrure de potassium*

Une solution de trinorlactone (II) (980 mg) dans 30 ml de dioxanne est traitée par une solution de borohydrure de potassium (360 mg) dans 20 ml de dioxanne aqueux (1 : 1). Après une nuit à température ordinaire, on détruit l'excès de réducteur par addition d'acide acétique et on dilue à l'eau. L'extraction par l'éther donne 1 g de résidu qui, par chromatographie sur alumine (benzène) et recristallisation (Chf-éther de pétrole), donne 900 mg de

3β-hydroxy trinor-dammarane 24:20ξ_2*-olide* (XIII, R = H):

$F =$ 205–206°; $[\alpha]_i$ +39° ($c = 1{,}4$; Chf).

$C_{27}H_{44}O_3$ (416,62)	Calc.%	C: 77,83	H: 10,65
	Trouvé	C: 77,67	H: 10,83

Acétylation. Par acétylation à froid, on obtient quantitativement le 3-acétate correspondant (XIII, R = Ac), recristallisé dans CH_2Cl_2–MeOH:

$F = 237$–$238°$; $[\alpha]_i$ +50° ($c = 1$; Chf).

$C_{29}H_{46}O_4$ (458,66)	Calc.%	C: 75,94	H: 10,11
	Trouvé	C: 75,96	H: 9,97

Action du bromure de phényl-magnésium sur l'acétate-lactone (XIII, R = Ac)

On prépare le réactif magnésien avec 7,2 g de magnésium, 47,1 g de bromobenzène et 150 ml d'éther. On ajoute en 1 heure environ, en maintenant un fort reflux, une solution de 13,8 g de lactone (XIII) dans 200 ml de benzène anhydre. Avant chaque nouvelle addition, on attend la redissolution du précipité initialement formé. On poursuit le reflux pendant 2 heures, puis, à 0° on détruit l'excès de réactif par du chlorure d'ammonium saturé et de la glace. On sépare la phase organique et on la lave à l'eau. On évapore les solvants sous vide, et on entraîne à la vapeur le diphényle,

le phénol, etc. formés. Le résidu non entraîné cristallise au refroidissement (13,5 g). Ce produit est recristallisé dans le benzène et l'éther de pétrole. C'est le

3β,20 ξ₂,24-trihydroxy 24,24-diphényl-trinor-dammarane (XIV, R = H):
$F = 194°$; $[\alpha]_j + 32°$ ($c = 1$; Chf).

$C_{39}H_{56}O_3$ (572,84)	Calc.%	C: 81,77	H: 9,85
	Trouvé	C: 81,72	H: 9,97

Acétylation. L'acétylation donne le 3-acétate correspondant (XIV, R = Ac), recristallisé dans l'éther de pétrole en paillettes [rendement global à partir de la lactone (XIII, R = Ac): 70%]:
$F = 185$–$186°$; $[\alpha]_j + 34°$ ($c = 1$; Chf)

$C_{41}H_{58}O_4$ (614,87)	Calc.%	C: 80,08	H: 9,51
	Trouvé	C: 80,02	H: 9,56

Spectre U.V.: λ_{max}^{EtOH} 243 ($\varepsilon = 328$), 249 ($\varepsilon = 424$), 255 ($\varepsilon = 511$), **259** ($\varepsilon = 677$), 265 mμ ($\varepsilon = 461$).

Déshydratation de l'acétate-diol (XIV, R = Ac)

On dissout 800 mg de l'acétate-diol (XIV, R = Ac) dans 40 ml d'acide acétique; on ajoute 80 mg d'acide *p*-toluène-sulfonique, et on porte à 80°. On suit le cours de la déshydratation en prélevant toutes les heures, 0,01 ml, que l'on dilue à 10 ml à l'éthanol, et en examinant l'absorption autour de 304 mμ. Après 6 heures, ε n'augmente plus sensiblement. On laisse refroidir, et on dilue à l'eau. Le précipité qui se sépare est filtré, et le filtrat est extrait à l'éther. L'ensemble des fractions ainsi isolées est chromatographié sur alumine (60 g). On élue:

(A)—par l'éther de pétrole-benzène (9 : 1): 545 mg (73%) de *diène* (XV), R = Ac).

(B)—par l'éther de pétrole-benzène (1 : 1): 200 mg (26%) du composé *tétrahydrofurannique* (XVI, R = Ac).

(A)—Le *3β-acétoxy 24,24-diphényl-trinor-dammara*-20(22),23-*diène* (XV, R = Ac) est cristallisé dans CH_2Cl_2–MeOH:
$F = 120$–$123°$; $[\alpha]_j + 4°$ ($c = 2$; Chf).

$C_{41}H_{54}O_2$ (578,84)	Calc.%	C: 85,07	H: 9,41
	Trouvé	C: 85,37	H: 9,38

Spectre U.V.: λ_{max}^{EtOH} 305 mμ ($\varepsilon = 28.200$)
$\lambda_{max}^{CH_2Cl_2}$ 262 ($\varepsilon = 11.000$), **304** ($\varepsilon = 27.100$), 306 ($\varepsilon = 27.000$), 310 mμ ($\varepsilon = 26.900$).

Saponification. Le diène-acétate précédent (360 mg) est saponifié par reflux (90 min) de sa solution dans le dioxanne (10 ml) et le méthanol (10 ml) avec 600 mg de potasse. Après traitement habituel et chromatographie sur alumine (20 g; Bz), on obtient 290 mg de produit incolore amorphe, l'alcool (XV, R = H):
$[\alpha]_j - 7°$ ($c = 2$; Chf).

$C_{39}H_{52}O$ (536,81)	Calc.%	C: 87,25	H: 9,77
	Trouvé	C: 87,03	H: 9,77

(B)—*Le 3β-acétoxy 20 ξ$_2$:24-époxy 24,24-diphényl-trinor-dammarane* (XVI, R = Ac) est recristallisé dans Chf–MeOH:

F = 231–231,5°; $[\alpha]_j$ +24° (c = 1,2; Chf)

$C_{41}H_{56}O_3$ (596,86)	Calc.%	C: 82,50	H: 9,46
	Trouvé	C: 81,94	H: 9,64

Spectre U.V.: λ_{max}^{EtOH} 260 mμ (ε = 875).

Saponification. Le mode opératoire précédent donne l'alcool correspondant: (XVI, R = H), qui est recristallisé dans Chf-éther de pétrole:

F = 195°; $[\alpha]_j$ +12° (c = 2; Chf).

$C_{39}H_{54}O_2$ (554,82)	Calc.%	C: 84,42	H: 9,81
	Trouvé	C: 84,45	H: 9,79

Déshydratation partielle de l'acétate-diol (XIV, R = Ac)

On dissout 500 mg de l'acétate-diol (XIV, R = Ac) dans 10 ml d'acide acétique. On ajoute une solution de 800 mg de dihydrate de bichromate de sodium dans 10 ml d'acide acétique, à 25°. En quelques minutes apparaissent des cristaux qui croissent rapidement; on laisse reposer quelques heures, et on filtre le précipité. Après recristallisation (Chf–MeOH), on obtient 458 mg (94%) du dérivé tétrahydrofurannique (XVI, R = Ac).

Par l'acide oxalique dans l'acide acétique, à reflux sous azote, on obtient en 7,5 heures, environ 20% de diène, en 38 heures, 30% de diène. Ces rendements sont indiqués par mesure de l'intensité d'absorption à 304 mμ, et confirmés par isolement; le tétrahydrofuranne (XVI) est isolé avec un rendement de 70% environ après 38 heures.

Passage du dérivé tétrahydrofurannique (XIV) *au diène* (XV)

On dissout 1 g du dérivé tétrahydrofurannique (XIV, R = Ac) dans 50 ml d'acide acétique; on ajoute 90 mg d'acide *p*-toluène-sulfonique et on porte à 80°. On suit la proportion de diène formé, par l'intensité de la bande d'absorption à 304 mμ:

Durée :	2h :	4h :	6h :	8h :	23h :
Diène formé :	9% :	17% :	25% :	33% :	57% :

Après 24 heures on dilue à l'eau; on chromatographie le produit obtenu, et on isole ainsi 56% de diène (XV, R = Ac), et 40% du tétrahydrofuranne de départ.

Oxydation du diène (XV) *en méthyl-cétone* (VII)

On dissout 310 mg du diène (XV, R = Ac) dans 10 ml de chlorure de méthylène et 10 ml d'acide acétique glacial. On refroidit par de la glace, et on ajoute, en 15 min, avec agitation magnétique, une solution de 250 mg de CrO_3 dans 0,4 ml d'eau et 2 ml d'acide acétique. On agite encore 1 heure à 0° et on détruit l'excès d'acide chromique par une solution de métabisulfite de sodium. On élimine la plus grande partie des solvants sous vide, et on reprend le résidu par le minimum de chlorure de méthylène, dilué ensuite à l'éther. Le produit isolé de la façon habituelle est chromatographié sur alumine.

On obtient en tête (éther de pétrole) 69 mg d'une huile incolore qui, rechromatographiée, cristallise: $F = 40$–$47°$; c'est la *β,β-diphénylacroléine*.[18] Cette identification est confirmée par la préparation d'une 2,4-dinitrophénylhydrazone rouge, $F = 195°$.[19]

L'éther de pétrole, puis les mélanges éther de pétrole-benzène, éluent ensuite des fractions cristallines identiques, recristallisées dans le méthanol: 181 mg (92%) de *3β-acétoxy 20-oxo hexanor-dammarane* (VII, R = Ac): $F = 204$–$205°$; $[\alpha]_j + 67°$ ($c = 1{,}2$; Chf), identifié par comparaison avec un échantillon authentique obtenu par la méthode de Mills[35].

Saponification. Par saponification à température ordinaire, on obtient le dérivé 3-hydroxy correspondant, déjà décrit par Mills[35] recristallisé dans l'éther de pétrole: $F = 195°$ (VII, R = H).

Saponification de l'acétate-lactone (XIII, R = Ac)

On saponifie comme d'habitude l'acétate-lactone (XIII, R = Ac) et on isole le précipité obtenu par dilution à l'eau et acidification lente par l'acide chlorhydrique dilué (acidité finale très faible). Le produit est cristallisé dans MeOH–H_2O: c'est le *3β,20ξ$_2$-dihydroxy trinor-dammarane 24-oïque* [correspondant à (XIII, R = H), lactone ouverte]:

$F = 180$–$183°$ (perte d'eau, puis resolidification) et 201–$202°$ (F de la lactone ci-après); $[\alpha]_j + 41°$ ($c = 1$, Di).

$C_{27}H_{46}O_4$ (434,64)	Calc. %	C: 74,61	H: 10,67
	Trouvé	C: 74,85	H: 10,59

Spectre I.R.: ν(C=O) 1706 cm^{-1} (Chf).

Si on acidifie franchement le mélange réactionnel résultant de la saponification *avant* la dilution à l'eau, ou si on traite une solution méthanolique de l'acide précédent par l'acide chlorhydrique dilué, on obtient la lactone correspondante; c'est le *3β-hydroxy trinor-dammarane 24:20ξ$_2$-olide* (XIII, R = H):

$F = 205$–$206°$; $[\alpha]_j + 39°$ ($c = 1{,}4$; Chf).

$C_{27}H_{44}O_3$ (416,62)	Calc. %	C: 77,83	H: 10,65
	Trouvé	C: 77,67	H: 10,83

Spectre I.R.: ν(C=O) 1765 cm^{-1} (Chf).

La *même* lactone est obtenue par réduction de la cétone-lactone (II) par le borohydrure de potassium dans le dioxanne aqueux (1 : 1). Son acétylation régénère l'acétate-lactone (XIII, R = Ac).

Contraction du cycle A sur l'hydroxy-lactone (XIII, R = H)

On dissout 2 g d'hydroxy-lactone (XIII, R = H) dans 400 ml de benzène anhydre; on distille 50 ml de benzène pour éliminer les traces d'eau. On refroidit par de la glace et de l'eau, et on ajoute en une fois 2,8 g de pentachlorure de phosphore sublimé, juste avant l'emploi, dans un tube à essais protégé contre l'humidité. On agite

[18] E. P. Kohler et R. G. Larsen, *J. Amer. Chem. Soc.* **57**, 1451 (1935).
[19] H. Lorenz et R. Wizinger, *Helv. Chim. Acta* **28**, 600 (1945); S. M. McElvain et L. R. Morris, *J. Amer. Chem. Soc.* **74** 2657 (1952).

magnétiquement pendant 1 heure, en faisant barboter un courant d'azote sec dans la solution. On verse ensuite la solution sur un volume égal de carbonate de sodium aqueux à 10%, et on agite violemment pendant 30 min. On lave plusieurs fois la couche organique à l'eau, et on la filtre sur quelques g d'alumine. On la sèche sur carbonate de sodium anhydre, et on évapore le benzène. On obtient 1,98 g d'une huile très peu colorée qui cristallise rapidement par refroidissement. On recristallise dans CH_2Cl_2-MeOH, et obtient le *A-néo-trinor-dammara*-3-*ène* 24:20ξ_2-*olide* (XVII):

$F = 168$–$170°$; $[\alpha]_i + 37°$ ($c = 1$; Di).

$C_{27}H_{42}O_2$ (398,61)	Calc.%	C: 81,35	H: 10,62
	Trouvé	C: 81,48	H: 10,52

Isomérisation du dérivé iso*propylidénique* (XVII)

Une solution de 500 mg du dérivé *iso*propylidénique précédent dans 5 ml de CH_2Cl_2 est traité par un courant de gaz chlorhydrique sec, à 10°. Après 2 heures, on lave à l'eau et au carbonate de sodium à 10% et on isole le produit. On filtre sur alumine, et on laisse le produit en présence d'un mélange de CH_2Cl_2 et d'éther de pétrole. Après plusieurs jours de repos, on obtient les cristaux incolores du *A-néo-trinor-dammara*-3(5)-*ène* 24:20ξ_2-*olide* (XVIII).

$F = 108$–$112°$; $[\alpha]_i + 56°$ ($c = 1$; Chf) (test de Beilstein très faiblement positif; homogénéité imparfaite).

$C_{27}H_{42}O_2$ (398,61)	Calc.%	C: 81,35	H: 10,62
	Trouvé	C: 80,99; 80,60	H: 11,17; 10,71

Par action de PCl_5 sur l'hydroxy-lactone (XIII, R = H) dans les mêmes conditions que précédemment, sous azote mais sans barbotage, on isole un mélange des deux composés éthyléniques précédents.

Ozonisation du dérivé iso*propylidénique* (XVII)

On refroidit à $-70°$ une solution de 1,5 g de lactone éthylénique (XVII) dans 20 ml de $CH Cl_2$; on fait passer un courant d'oxygène ozonisé jusqu'à coloration bleue (test au tétranitrométhane négatif). A température ordinaire, on ajoute 10 ml d'acide acétique et, avec agitation magnétique, 3 g de zinc en poudre, par petites portions. On laisse réagir jusqu'à test négatif au papier iodo-amidonné. Le produit isolé est alors chromatographié lentement sur alumine (25 g). On obtient à l'éther de pétrole-Bz (1 : 1) 920 mg de *cétone-lactone* (XIX), $F = 190°$, puis à MeOH–AcOH (9:1), 550 mg de l'*hydroxy-acide* correspondant (XIX, lactone ouverte). Ce dernier est recristallisé dans le méthanol: $F = 205$–$207°$; traité par une trace d'acide chlorhydrique dans le méthanol, puis chromatographié rapidement, il est élué à l'éther de pétrole-Bz (1:1) et est alors identique à la cétone lactone (XIX).

On recristallise dans CH_2Cl_2–MeOH le 3-*oxo trinor-A*(4)-*trinor*-(5β)*dammarane* 24:20ξ_2-*olide* (XIX):

$F = 194$–$196°$; $[\alpha]_i + 185°$ ($c = 1$; Chf).

$C_{24}H_{36}O_3$ (372,53)	Calc.%	C: 77,37	H: 9,74
	Trouvé	C: 77,46	H: 9,86

Spectre U.V.: λ_{max}^{CH} 279 ($\varepsilon = 33$). **288** ($\varepsilon = 35$), 299 ($\varepsilon = 34$), 310 mμ ($\varepsilon = 28$)*

Contraction du cycle A sur l'hydroxy-cétone (VII, R = H)

On suit le mode opératoire détaillé ci-dessus pour l'hydroxy-lactone (XIII, R = H). A partir de 1 g d'hydroxy-cétone (VII, R = H), on obtient, après chromatographie du produit de raction avec PCl_5, 700 mg élués à l'éther de pétrole, cristallisant dans MeOH. C'est le 20-*oxo A-néo-hexanor-dammara*-3-*ène* (XX):

$F = 120$–$121°$; $[\alpha]_j + 52°$ ($c = 0{,}9$; Di).

$C_{24}H_{38}O$ (342,54)	Calc %	C: 84,15	H: 11,18
	Trouvé	C: 84,11	H: 11,20

Isomérisation du dérivé iso*propylidénique* (XX)

Par action de gaz chlorhydrique sur une solution du dérivé *iso*propylidénique (XX) dans le méthanol (0°; 20 min), on obtient son isomère, cristallisant dans le méthanol: le 20-*oxo A-néo-hexanor-dammara*-3(5)-*ène* (XXI):

$F = 72{,}5$–$74°$; $[\alpha]_j + 102°$ ($c = 1$; Chf).

$C_{24}H_{38}O$ (342,54)	Calc %	C: 84,15	H: 11,18
	Trouvé	C: 84,00	H: 11,32

Par simple recristallisation du dérivé *iso*propylidénique dans Chf–MeOH, on observe un étalement progressif du point de fusion, qui tend vers 75° (traces d'acidité du chloroforme)

Ozonisation du dérivé iso*propylidénique* (XX)

On suit le mode opératoire précédemment décrit sur le composé (XVII) La chromatographie du produit de l'ozonisation de 700 mg d'éthylénique (XX), sur 40 g d'alumine, donne: A—220 mg de produit cristallisé $F = 155°$ (Kof.), élué à Bz–Et_2O (9 : 1), B—225 mg de produit amorphe, élué à MeOH–AcOH (9 : 1).

A—Par recristallisation dans le méthanol, on obtient le 3,20-*dioxo hexanor-A*(4) *trinor*-(5β)*dammarane* (XXII):

$F = 156$–$158°$; $[\alpha]_j + 195°$ ($c = 1$; Chf).

$C_{21}H_{32}O_2$ (316,46)	Calc. %	C: 79,69	H: 10,20
	Trouvé	C: 79,52	H: 10,24

B—Le produit amorphe, acide, obtenu en fin de chromatographie, présente dans son spectre I.R. deux bandes ν(C=O): 1690 cm^{-1} et 1739 cm^{-1}; après traitement au diazométhane, seule la bande vers 1740 cm^{-1} subsiste (*cyclo*pentanone et ester), mais le produit n'a pas non plus été obtenu cristallisé. Il s'agit probablement de l'acide en C-20. Harries[21] a décrit des cas analogues de coupure de cétones en acides par ozonisation poussée.

Réaction de l'acide trifluoroperacétique sur l'hydroxy-méthylcétone (VII, R = H)

A 1,5 ml de peroxyde d'hydrogène à 85%, en suspension dans 50 ml de chlorure

* D'observations non publiées de M. C. Sandris, dans notre laboratoire, il résulte que les *cyclo*pentanones substituées, comme la cyclopentanone elle-même, présentent dans un solvant non-polaire une structure fine caractéristique de leur bande d'absorption vers 290 mμ.

[21] C. Harries, *Liehigs Ann.* **374**, 288 (1910).

de méthylène anhydre, on ajoute en une seule fois 9 ml d'anhydride trifluoracétique, à 0°. Après quelques instants, on laisse revenir à température ambiante en agitant: le peracide se forme, et une observation attentive permet de suivre le passage en solution du peroxyde d'hydrogène. Dès que la solution est homogène, on l'ajoute en 15 min à une solution de 3,17 g de méthyl cétone (VII, R = H) dans 50 ml de CH_2Cl_2 anhydre, contenant en suspension 24 g de phosphate disodique anhydre. On effectue cette addition à température ordinaire, en agitant manuellement, et en refroidissant de temps à autre dans l'eau glacée.

On ajoute ensuite prudemment (dégagement de CO_2) et en refroidissant, une solution aqueuse de carbonate de sodium à 10%, puis 200 ml d'éther. La phase organique est séchée et évaporée; on obtient 3,59 g d'huile incolore que l'on chromatographie sur 100 g d'alumine. On élue:

A—à l'éther: 2,54 g (77%) d'un composé cristallisé, $F = 195°$ (Kof.).

B—à l'éther aussi, environ 800 mg de produit cristallisant lentement et fondant à 200° (Kof.).

A—La première fraction, par recristallisation dans l'éther, donne le *3β-hydroxy 17β?-acétoxy octanor-dammarane* (XXIII, R = H, R′ = Ac):

$F = 198$–$199{,}5°$; $[\alpha]_j$ +54° ($c = 1$; Chf)

$C_{24}H_{40}O_3$ (376,56):	Calc.%	C: 76,55	H: 10,70
	Trouvé	C: 76,52	H: 10,83

B—La seconde fraction est recristallisée dans MeOH–H_2O, et identifiée au diol (XXIII, R = R′ = H) ci-dessous, par fusion de mélange et I.R.

Saponification. On procède comme d'habitude et on isole après recristallisation dans MeOH–H_2O le diol (XXIII, R = R′ = H):

$F = 209$–$210°$; $[\alpha]_j$ +47° ($c = 1$; Chf)

$C_{22}H_{38}O_2$ (334,52)	Calc.%	C: 78,99	H: 11,45
	Trouvé	C: 78,24	H: 11,48

Acétylation. L'acétylation pyridinée de l'hydroxy-acétate (XXIII, R = H, R′ = Ac) donne quantitativement le diacétate (XXIII, R = R′ = Ac), recristallisé dans MeOH–H_2O:

$F = 161°$; $[\alpha]_j$ +59° ($c = 1$; Chf)

$C_{26}H_{42}O_4$ (418,60):	Calc.%	C: 74,60	H: 10,11
	Trouvé	C: 74,41	H: 10,12

Contraction du cycle A sur l'hydroxy-acétate (XXIII, R = H, R′ = Ac)

On suit le mode opératoire détaillé ci-dessus pour l'hydroxy-lactone (XIII, R = H). A partir de 2 g d'hydroxy-acétate (XXIII, R = H, R′ = Ac), on obtient après chromatographie du produit de réaction avec PCl_5 1,14 g (60%) de produit élué à l'éther de pétrole, cristallisant dans le méthanol. C'est le *17β?-acétoxy A-néo-octanor-dammara-3-ène* (XXIV, R = Ac):

$F = 141{,}5$–$143°$; $[\alpha]_j$ +43° ($c = 1$; Di)

$C_{21}H_{38}O_2$ (358,54)	Calc.%	C: 80,39	H: 10,68
	Trouvé	C: 80,44	H: 10,63

Saponification. On procède comme d'habitude et on isole, après chromatographie sur alumine (Bz–Et_2O 1 : 1) et recristallisation dans MeOH–H_2O, l'alcool (XXIV, R = H):

F = 125–126°; $[\alpha]_j$ +32° (c = 1; Di)

$C_{22}H_{36}O$ (316,51)	Calc.%	C: 83,48	H: 11,47
	Trouvé	C: 82,75	H: 11,52

Ozonisation du dérivé isopropylidénique (XXIV, R = Ac)

On suit mode opératoire précédemment décrit pour le composé (XVII). On part de 880 mg du composé (XXIV, R = Ac); la chromatrographie du produit brut d'ozonisation, sur 20 g d'alumine, donne 513 mg (62%) de produit F = 177–179°. Par recristallisation dans MeOH, on obtient le 17β?-*acétoxy* 3-*oxo octanor-A*(4)-*trinor*-(5β)*dammarane* (XXV, R = Ac):

F = 185–187°; $[\alpha]_j$ +185° (c = 1; Chf)

$C_{21}H_{32}O_3$ (332,47)	Calc.%	C: 75,86	H: 9,70
	Trouvé	C: 75,63	H: 9,71

Saponification. On suit le mode opératoire habituel, et on isole après recristallisation dans le méthanol l'alcool-cétone (XXV, R = H):

F = 127–128°; $[\alpha]_j$ +213° (c = 1; Chf)

$C_{19}H_{30}O_2$ (290,43)	Calc.%	C: 78,57	H: 10,41
	Trouvé	C: 78,29	H: 10,76

Action de l'iodure de méthyl-magnésium sur la cétone (XXV, R = Ac)

On filtre sur coton le réactif magnésien obtenu à partir de 2,25 g de magnésium et environ 6 ml d'iodure de méthyle dans 20 ml d'éther anhydre. On ajoute, au reflux de l'éther, une solution de 333 mg de cétone-acétate (XXV, R = Ac) dans 20 ml de benzène. On laisse à reflux pendant 48 heures, on distille l'éther et on laisse encore 1 heure au reflux dans le benzène. On isole le produit de la façon habituelle, et on obtient 324 mg d'huile qui est immédiatement acétylée avec 4 ml de pyridine et 5 ml d'anhydride acétique. On isole 360 mg de produit cristallisant lentement, qui est chromatographié sur alumine (10 g). On obtient:

A—112 mg élués à l'éther de pétrole, huileux.

B—77 mg élués à éther de pétrole-Et_2O (10 : 1), F env. 180° (Kof.).

C—139 mg élués à éther de pétrole–Et_2O (5 : 1), F env. 150° (Kof.).

A—La première fraction présente en I.R. les bandes caractéristiques d'une fonction acétate, et une réaction positive au tétranitrométhane; il est probable que c'est un produit de déshydratation de l'alcool tertiaire attendu, par l'iodure de magnésium présent. Nous n'avons pas étudié davantage cette fraction.

B—La seconde fraction est identifiée au produit de départ; elle est plus importante dans les essais faits avec une durée moindre de reflux, et exclusive dans les essais faits avec uniquement de l'éther, ou avec MeLi dans le tétrahydrofuranne.

C—La troisième fraction est recristallisée dans l'éther de pétrole, et donne le

3β?-hydroxy 17β?-acétoxy 3α-méthyl octanor-A(4)-trinor-(5β)-dammarane (XXVI, R = Ac):

$F = 153$–$155°$; $[\alpha]_j$ $+31°$ ($c = 0{,}3$; Chf)

$C_{22}H_{36}O_3$ (348,51)	Calc.%	C: 75,81	H: 10,41
	Trouvé	C: 75,96	H: 10,87

Saponification. On suit le mode opératoire habituel, et on isole après chromatographie sur alumine (éther de pétrole — Et_2O 1 : 1) et recristallisation dans l'éther de pétrole le diol (XXVI, R = H):

$F = 145$–$148°$; $[\alpha]_j$ $+36°$ ($c = 0{,}5$; Chf).

$C_{20}H_{34}O_2$ (306,47)	Calc.%	C: 78,38	H: 11,18
	Trouvé	C: 78,46	H: 11,39

Déshydratation de l'alcool tertiaire (XXVI, R = Ac)

On prépare par barbotage une solution saturée de gaz chlorhydrique sec dans 10 ml de chloroforme anhydre; on y dissout 100 mg de l'alcool-acétate (XXVI, R = Ac). On suit, sur un prélèvement ultérieurement réuni au reste de la solution, la variation du pouvoir rotatoire qui passe de $+30°$ à $+75°$ après une heure à température ordinaire. On jette alors dans l'eau, et on isole le produit par extraction. On obtient 98 mg d'une huile qui est chromatographiée sur 5 g d'alumine. L'éther de pétrole élue 80 mg (84%) de produit $F = 85°$ (Kof.), recristallisé dans MeOH. C'est le *17β?-acétoxy 3-méthyl-octanor-A(4)-trinor-dammara-3(5)-ène* (XXVII, R = Ac): $F = 90$–$91°$; $[\alpha]_j$ $+75°$ ($c = 1$; Chf).

$C_{22}H_{34}O_2$ (330,49)	Calc.%	C: 79,95	H: 10,37
	Trouvé	C: 79,44	H: 10 46 (L.L.)

Hydroxylation du composé (XXVII, R = Ac)

On ajoute une solution de 100 mg de tétroxyde d'osmium dans 5 ml d'éther, à une solution de 80 mg du composé (XXVII, R = Ac) dans 5 ml d'éther et 0,3 ml de pyridine. Après 4 jours à température ambiante, on évapore à sec sous vide; on reprend le résidu brun dans 10 ml de benzène anhydre, et on traite par un excès d'hydrure de lithium et d'aluminium dans l'éther. On isole, de la façon habituelle, 87 mg de produit qui est recristallisé dans l'éther. C'est le *3α,5α,17β?-trihydroxy 3-méthyl-octanor-A (4)-trinor-dammarane* (XXVIII, R = H): $F = 126$–$128°$ (perte de solvant) et 161–$163°$ (161–$163°$ après séchage sous vide à $50°$); $[\alpha]_j$ $+20°$ ($c = 85$; Chf).

$C_{20}H_{34}O_3$ (322,47)	Calc.%	C: 74,49	H: 10,63
	Trouvé	C: 74,52	H: 10,66 (L.L.)

Acétylation. On suit le mode opératorie habituel, et le produit obtenu est recristallisé dans l'éther. On a ainsi le dihydroxy-acétate (XXVIII, R = Ac):

$F = 138$–$139°$; $[\alpha]_j$ $+28°$ ($c = 0{,}8$; Chf)

$C_{22}H_{36}O_4$ (364,51)	Calc.%	C: 72,49	H: 9,96
	Trouvé	C: 72,54	H: 10,13 (L.L.)

Coupure du glycol (XXVIII) *et recyclisation*

On ajoute, à 87 mg du glycol (XXVIII, R = H) dissous dans 5 ml de chloroforme, une solution de 96 mg de tétracétate de plomb dans 5 ml d'acide acétique. En 1 heure à température ordinaire, tout le tétracétate est consommé (test au papier iodo-amidonné). On ajoute encore 1 ml d'acide acétique contenant 24 mg de tétracétate, et on laisse réagir une nuit; il subsiste un excès de tétracétate, que l'on détruit par une goutte d'éthylène-glycol. On isole le produit de la facon habituelle, et on obtient 90 mg d'une huile jaune-pâle, considérée comme contenant la dicétone (XXIX).

On ajoute 10 ml de potasse méthanolique à 10%, à 80 mg de *testostérone* (solution témoin) et 10 ml au produit précédent. On porte le témoin quelques minutes à 80°; l'intense coloration jaune de l'énolate apparaît rapidement. On chauffe de la même façon la solution contenant la dicétone, jusqu'à obtention d'une couleur jaune comparable. On laisse encore 1 heure au repos, et on vérifie que le coefficient d'extinction à 242 mμ correspond à une réaction totale, par comparaison avec la testostérone (prélèvement de 0,01 ml). On isole le produit de la façon habituelle, et on obtient 96 mg d'une huile qui est chromatographiée sur 5 g d'alumine. Par élution au benzène-éther (10 : 1), on obtient 62 mg de cristaux F = 192–194°, recristallisés dans l'éther de pétrole. C'est la 8,14 diméthyl 18-nor-testostérone: *17β?-hydroxy 3-oxo octanor-28,29-dinor-dammara-4-ène* (XXX, R = H):

F = 208–210°; $[\alpha]_j$ +140° (c = 1,1; Chf).

$C_{20}H_{30}O_2$ (302,44)	Calc.%	C: 79,42	H: 10,00	
$C_{20}H_{31}O_2$, $\frac{1}{2}H_2O$ (311,45)		C: 77,18	H: 10,04	
	Trouvé*	C: 77,09	H: 9,75 (L.L.)	
		C: 78,65; 78,74	H: 9,94; 10,27	

Spectre U.V. : λ_{max}^{EtOH} 242 mμ (ε = 19.300)

Spectre I.R. ν(O—H) 3600 cm^{-1}; ν(C=O): 1670 cm^{-1}; ν(C=C): 1620 cm^{-1}(CH_2Cl_2)

Action de l'iodure de méthyl-magnésium sur la nor-cétone (VIII)

On prépare le réactif magnésien avec 250 mg de magnésium et 1 ml d'iodure de méthyle dans 10 ml d'éther; on ajoute 239 mg de la nor-cétone acétate (VIII, R = Ac). Le précipité qui se forme immédiatement est redissous par addition de 10 ml de benzène, et chauffage à reflux. Après 3 heures, on décompose l'excès de réactif et on isole le produit de la façon habituelle. Les 246 mg obtenus sont acétylés à température ordinaire, et les acétates obtenus sont chromatographiés sur alumine (9 g). On élue au benzène-éther de pétrole (1 : 9 à 1 : 1) 185 mg au total de fractions cristallines, de point de fusion mal défini vers 100°. On recristallise séparément ces fractions dans MeOH–H_2O; les cristaux obtenus fondent, après une nouvelle recristallisation une fois réunis, à 104–106°, pas déprimé par mélange avec un échantillon authentique de l'acétate (IV, R = Ac), F = 106–108°, obtenu à partir du diptérocarpol comme indiqué par Mills[36] ("Dammarane-diol-II monoacétate"); l'identité est confirmée par comparaison des spectres I.R. dans le Nujol: 16 bandes, toutes identiques, en dehors des bandes du Nujol.

Les eaux-mères de cristallisation sont réunies et soumises à une triangulation par cristallisation dans MeOH–H_2O et dans le nitrométhane. On isole ainsi une petite

* Sur deux échantillons différents; conditions de séchage non notées.

quantité de produit fondant à 142–144°. Il s'agit sans doute de l'épimère en C-20 de l'acétate (IV, R = Ac), décrit par Mills ("Dammarane-diol-I monoacétate", F = 145–147°), mais l'identification n'a pu être faite avec certitude.

Passage du mélange des acétates éthyléniques (V) *et* (IV) (R = Ac) *au diol* (XXIII; R = R′ = H) (par J. F. Biellmann).

Le mélange des éthyléniques de départ est obtenu par la méthode de Mills[3b]; il contient, d'après Mills, environ 50% de chaque isomère, ce que nous avons vérifié par ailleurs, par séparation chromatographique soignée des cétones de coupure (VII) et (VIII).

On ozonise une solution de 5 g du mélange des oléfines (V) et (VI) (R = Ac) dans 20 ml de chlorure de méthylène et 100 ml d'acide acétique. Après 1 heure d'ozonisation à température ordinaire, un test au tétranitrométhane étant négatif, on procède à la décomposition des ozonides par addition d'eau et chauffage à 80° pendant 45 min. On fait passer à chaud un courant d'air à travers la solution, devenue laiteuse. Le mélange des cétones de coupure cristallise. On le filtre et le lave à l'eau. Après séchage, on obtient 4,8 g de produit brut, qui est filtré sur 48 g d'alumine. On élue en tout (éther-de pétrole–Et_2O) 3,48 g de mélange purifié des deux cétones-acétates (VII) et (VIII) (R = Ac), directement utilisé pour l'étape suivante.

On effectue sur le mélange des cétones précédentes la coupure à l'acide trifluoroperacétique: la solution d'acide trifluoroperacétique utilisée est préparée à partir de 0,64 ml de peroxyde d'hydrogène à 85% et 3,6 ml d'anhydride trifluoroacétique dans 45 ml de chlorure de méthylène. On ajoute en une fois, à 0°, cette solution à une solution de 3,48 g du mélange des cétones précédentes dans 40 ml de chlorure de méthylène contenant en suspension 6,15 g de phosphate disodique pulvérisé anhydre. On laisse revenir à température ordinaire; après15 min, on décompose par addition de carbonate de sodium à 10%. On isole le produit: 3,6 g de mélange brut des di-esters (XXIII) (R = Ac, R′ = C_6H_{13}–CO– et R = R′ = Ac).

On saponifie directement ce mélange par traitement avec 1,5 g de soude dans 15 ml d'éthanol à 95%. Après 1 heure de chauffage à reflux, on dilue à l'eau, et on isole le produit cristallisé qui se sépare: 2,59 g de produit brut, qui est filtré sur alumine (25 g) et donne ainsi 2,20 g de diol (XXIII, R = R′ = H), identifié par point de fusion et point de fusion de mélange. Le rendement *global* à partir du mélange des éthyléniques de départ est de 62%.

Note ajoutée à la correction des épreuves: Les résultats décrits dans la communication suivante ont levé l'ambiguïté relative aux configurations en C-17. Dans tous les cas où nous avions indiqué une configuration probable 17β?, il convient donc de ne pas tenir compte du signe ?.

Tetrahedron, 1958, Vol. 3, pp. 303–309. Pergamon Press Ltd., London

LE DIPTÉROCARPOL—II*

STÉRÉOCHIMIE EN C-13 ET EN C-17

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Résumé—On décrit une série de transformations du cycle D du diptérocarpol ('hydroxy-dammarénone-II'), prouvant pour ce triterpène la configuration 13β, 17αH proposée antérieurement.

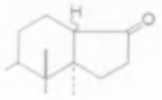
Abstract—Various reactions of ring D of dipterocarpol (hydroxy-dammarenone-II) show this triterpene to have the configuration 13β, 17αH, in accordance with biogenetic speculations.

NOUS avons précédemment décrit l'isolement du diptérocarpol (I), et sa transformation par étapes en l'analogue (II) de la testostérone.[1] Cette transformation utilisait comme intermédiaires deux cétones, (III) et (IV), dont la configuration en 17 est:

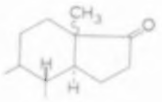
— *d'une part*—identique: (III) et (IV) ont été transformés stéréospécifiquement en le même dialcool (V, R = R′ = H)

— *d'autre part*—la configuration stable: ceci avait déjà été montré par Mills,[2] par traitement en milieu alcalin

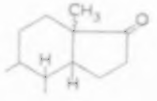
— *enfin*—la même que celle du diptérocarpol: la cétone (III) avait été transformée en alcool (VI), dérivant directement du diptérocarpol.



A



B



C

En outre, le groupe alcool ou ester en C-17 dans les dérivés (V) possède aussi cette même configuration, étant donnée la nature stéréospécifique de la réaction de coupure aux peracides utilisée pour leur formation.

Nous avions conclu de ces arguments, et d'une considération de modèles, que

* Cf. réf. 1.

† Boursier du CNRS (1957–1958).

‡ Boursier post-doctoral du CNRS (1956) et de l'IRSIA (1957).

[1] P. Crabbé, G. Ourisson et T. Takahashi, *Tetrahedron* **3**, 279 (1958).

[2] J. S. Mills, *J. Chem. Soc.* 2196 (1956).

deux arrangements stéréochimiques en C-13 et C-17 sont possibles: (A) et (B). Le premier, (A), qui correspond pour (II) à la stéréochimie de la testostérone, est seul conciliable avec les règles stéréochimiques proposées par Eschenmoser *et al.*,[3] pour la biogénèse des triterpènes, mais nous n'en apportons que maintenant la démonstration.

TABLEAU 1. ROTATIONS MOLÉCULAIRES DES 17-CÉTONES ÉPIMÈRES EN C-13 (ARRONDIES À ±2,5 UNITÉS).

	13 α	13 β	$\Delta_{\beta-\alpha}$	Réf.
	M_i −185	M_i +365	Δ_{M_i} +550	*a*
			Δ_{M_D} +535 à +565	*b,c*
			Δ_{M_D} +520	*c*

Réf.: *a*: cf. Partie Expérimentale; *b*: cf. L. F. Fieser et M. Fieser, *Natural Products Related to Phenanthrene* (3ème Ed.) p. 213. Reinhold Publishing Corporation, New York (1949); *c*: J. R. Billeter et K. Miescher, *Helv. Chim. Acta* **34**, 2053 (1951).

Par saponification partielle du diacétate (V, R = R′ = Ac) ou de son mélange avec l'acétate-*iso*heptylate (V, R = Ac, R′ = $C_6H_{13}CO$) obtenus comme nous l'avons indiqué précédemment,[1] on libère sélectivement la fonction en C-17, et on obtient le monoacétate en C-3 (V, R = Ac, R′ = H). La fonction alcoolique en C-17 peut être oxydée à froid par le bichromate de sodium en solution acétique,[4] et on isole ainsi la *monocétone* (VII, R = Ac).

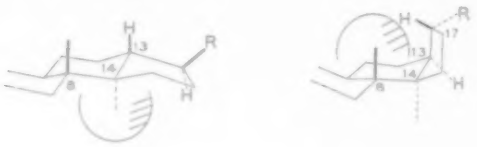
Dans cette oxydation, la configuration en C-13 n'a pas encore été modifiée, comme le prouve la série de réactions suivante:

Par réduction par le borohydrure de potassium et acétylation, la cétone (VII, R = Ac) donne un diacétate (VIII, R = R′ = Ac), *différant* de son isomère (V, R = R′ = Ac) par une inversion de la configuration en C-17. En effet, le 3-acétate 17-mésylate (V, R = Ac, R′ = Més), par traitement avec l'acétate de sodium dans l'acide

[3] A. Eschenmoser, L. Ruzicka, O. Jeger et D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955).
[4] L. F. Fieser, *J. Amer. Chem. Soc.* **75**, 4377 (1953).

acétique, donne bien le diacétate (VIII, R = R′ = Ac), identifié par ses constantes, l'épreuve de mélange, et la comparaison des spectres d'absorption infra-rouge. Comme souvent dans de telles réactions d'acétolyse, la substitution avec inversion est accompagnée d'élimination: le mélange de composés éthyléniques (IX, R = Ac) est le produit principal de la réaction.

La monocétone (VII, R = Ac) a donc encore en C-13 la configuration initiale. Or, il s'agit certainement d'un dérivé *trans*-hydrindanonique, de configuration 13β, 14α. Ceci découle de la comparaison de sa rotation moléculaire avec celle de son *épimère en* C-13, comme le montre le Tableau 1. Cet épimère en C-13, (X, R = Ac), est obtenu par traitement de la *trans*-cétone (VII) en milieu alcalin: du mélange obtenu, on sépare par chromatographie sur alumine neutre le constituant principal, la cétone *cis* (X). Le pouvoir rotatoire du mélange à l'équilibre des deux cétones indique que ce mélange contient environ 92% de cétone *cis*. Cette proportion est à rapprocher des nombreux cas connus d'hydrindanones dans un système A-nor-stéroide ou triterpénoïde, où seul l'isomère *cis* (5β) pratiquement pur a été caractérisé après traitement équilibrant. Cette différence de comportement était prévue, et nous pensons qu'elle provient de l'interaction de C-17, dans la cétone (X), avec le groupe méthyle β axial situé en C-8, comme le montre le schéma B. Dans le cas des dérivés A-nor, en l'absence de groupe 9α-méthyle, cette interaction n'existe pas, et la forme *cis*-hydrindanonique n'est pas partiellement déstabilisée.



A B

D

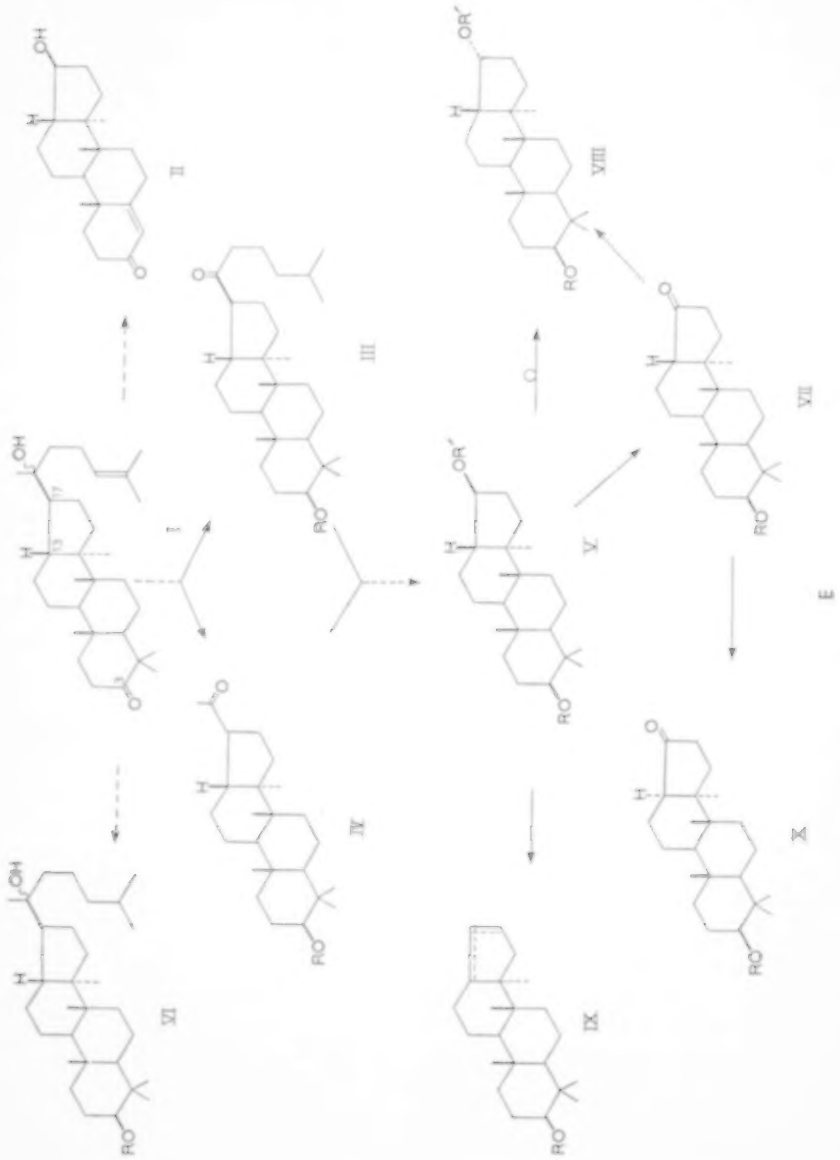
La considération de modèles moléculaires à l'échelle ou du schéma A explique que la réduction par le borohydrure conduise, dans le système (VII), à un alcool 17 α, par attaque du côté β; le groupe méthyle angulaire en C-14 protège le face α de la molécule au niveau du cycle D.

L'attribution des configurations 13β, 17αH, aux produits (I), (II), (III), (IV), (V), indiquée ci-dessus, dépend évidemment de la validité des comparaisons de rotations moléculaires faites ici; nous pensons que ces comparaisons sont justifiées sans aucun doute possible par l'importance des déplacements observés. L'ensemble des réactions décrites ici forme alors, du point de vue stéréochimique, un tout univoque.

La stéréochimie du diptérocarpol, et des autres produits de la famille du dammarane,[2] se trouve ainsi définie à tous les centres, *sauf* en C-20; nous ne prévoyons pas de nous attacher à résoudre ce dernier problème, sans grand intérêt puisque les *deux* séries naturelles épimères en C-20 ont été décrites par Mills.

PARTIE EXPÉRIMENTALE

Pour les indications générales, on se reportera à la communication précédente.[1] Les microanalyses ont été effectuées au Laboratoire de Microanalyse du CNRS de la Faculté des Sciences de Lyon (Professeur J. Colonge), par Monsieur Semet, que nous remercions vivement.



Obtention du monoacétate (V, R = Ac, R′ = H)

(1) *Par saponification partielle du diacétate* (V, R = R′ = Ac). On dissout 1,14 g (2,74 mmol) de 3β, 17β-diacétoxy octanor-dammarane (V, R = R′ = Ac), $F = 161°$[1] dans 100 ml d'éthanol; on ajoute 1 ml d'une solution normale de soude dans l'éthanol; après 2 heures, on ajoute encore 1 ml, après 12 heures, encore 0,74 ml (au total, 2,74 ml, soit 2,74 mmol). Après 24 heures à température ordinaire, on dilue à l'eau, on filtre, lave abondamment à l'eau et on sèche. Le produit brut (1,27 g) est chromatographié sur 60 g d'alumine. Le mélange éther de pétrole-éther (13:7) élue 700 mg d'un corps A; l'éther de pétrole-éther 1:1 élue 115 mg d'un corps B, $F = 211°$, identifié au diol (V, R = R′ = H).[1]

Le corps A est recristallisé dans le méthanol; c'est le *3β-acétoxy 17β-hydroxy octanor-dammarane* (V, R = Ac, R′ = H), $F = 174$–$175°$; $[\alpha]_j +50°$ ($c = 1$; Chf)

$C_{24}H_{40}O_3$ (376,56):	Calc. %	C:	76,55	H:	10,70
	Trouvé	C:	76,51	H:	10,50

(2) *Par saponification partielle du mélange des esters* (V, R = Ac, R′ = Ac et $C_6H_{11}CO$). On dissout 5,48 g du mélange (environ 1:1) des deux esters[1] dans 450 ml d'éthanol, et on ajoute à température ordinaire 9,75 ml de solution normale de soude dans l'éthanol, soit env. 80% d'un équivalent. Après 18 heures, on isole le produit selon le protocole habituel; le mélange huileux obtenu est chromatographié sur 275 g d'alumine. L'éther de pétrole-éther 19:1 élue une petite quantité de produit odorant, probablement l'isoheptanoate de méthyle formé par transestérification (50 mg). L'éther de pétrole-éther 1:1 élue le 3-acétate 17-hydroxy (V, R = Ac, R′ = H), $F = 174$–$175°$ (1,75 g). L'éther de pétrole-éther 3:7 élue le diol (160 mg); les fractions intermédiaires, (1,54 g) mal cristallisées, sont saponifiées et donnent ainsi le diol (V, R = R′ = H).

Oxydation de l'hydroxy-acétate (V, R = Ac, R′ = H)

On dissout 0,94 g de l'hydroxy-acétate (V, R = Ac, R′ = H) dans 35 ml d'acide acétique. A température ordinaire, on ajoute peu à peu une solution de 3 g de bichromate de sodium dans 5 ml d'acide acétique à 90%. Après 12 heures, on précipite par addition d'eau; le produit cristallisé qui est isolé par filtration est abondamment lavé et après séchage (0,85 g), est recristallisé dans CH_2Cl_2—MeOH; le *3β-acétoxy 17-oxo octanor-dammarane* (VII, R = Ac) ainsi formé est mal caractérisé par son point de fusion: $F = 224°$ (Kof.); 207–209° (cap. Pyrex); 189–199° (cap. verre ord.); ceci a été attribué à son épimérisation facile. $[\alpha]_j +98°$ ($c = 1$; Chf).

$C_{24}H_{38}O_3$ (374,54):	Calc. %	C:	76,96	H:	10,23
	Trouvé		77,79; 76,22		10,26; 10,39

Spectre U.V.: λ_{max}^{CH} 284, 286, **294** ($\varepsilon = 30$), 300 (ép.) mμ.

Spectre I.R.: ν(C=O): 1725 cm^{-1} (acétate, *cyclo*pentanone). (Chf.).

Réduction de l'acétoxy-cétone (VII, R = Ac)

On dissout 0,18 g d'acétoxy-cétone (VII, R = Ac) dans 40 ml de méthanol, et on ajoute 155 mg de borohydrure de potassium; après 1 heure à température ordinaire, on porte à reflux pendant 15 min, on décompose l'excès de réactif par quelques

gouttes d'acide acétique, et on dilue à l'eau. Le précipité cristallisé est filtré, lavé et séché (0,165 g). On le recristallise dans CH_2Cl_2—MeOH. C'est le *3β-acétoxy 17α-hydroxy octanor-dammarane* (VIII, R = Ac, R′ = H): $F = 179$–$180°$; $[\alpha]_j +23°$ ($c = 1$; Chf.).

$C_{24}H_{40}O_3$ (376,56):	Calc. %	C: 76,55	H: 10,71
	Trouvé	C: 76,53	H: 10,77

Acétylation. L'acétylation pyridinée de l'hydroxy-acétate (VIII, R = Ac, R′ = H) donne le *diacétate* (VIII, R = R′ = Ac): $F = 228$–$229°$; $[\alpha]_j +53°$ ($c = 0,9$; Chf.).

$C_{26}H_{42}O_4$ (418,63):	Calc. %	C: 74,60	H: 10,11
	Trouvé	C: 74,50	H: 10,13

Mésylation de l'hydroxy-acétate (V, R = Ac, R′ = H)

On dissout 0,32 g de l'hydroxy-acétate (V, R = Ac, R′ = H) dans 0,7 ml de pyridine; on ajoute cette solution à 0,5 ml de pyridine et 0,7 ml de chlorure de méthanesulfonyle, en refroidissant par de la glace. Après 15 heures, on ajoute de l'eau tout en refroidissant; on filtre, lave, sèche, et on recristallise dans CH_2Cl_2—MeOH en évitant de chauffer la solution (1ère recristallisation accompagnée de décoloration à l'Acticarbone). On obtient ainsi le *3β-acétoxy 17β-méthylsulfonyloxy octanor-dammarane* (V, R = Ac, R′ = Més): $F = 145°$ (Kof.; déc. dès 110°); $[\alpha]_j +55°$ ($c = 1$; Chf.).

$C_{25}H_{42}O_5S$ (454,65)	Calc. %	C: 66,08	H: 9,31
	Trouvé	C: 66,09	H: 9,21

Spectre I.R.: bande intense à 1167 cm^{-1}: (méthanesulfonate).

Acétolyse de l'acétate-mésylate (V, R = Ac, R′ = Més)

On chauffe à reflux pendant 4 heures une solution de 0,53 g du mésylate précédent et de 5 g d'acétate de potassium anhydre dans 15 ml d'acide acétique. Après refroidissement, on ajoute de l'eau, filtre, lave, et sèche. Le produit brut obtenu (0,41 g) donne un test positif au tétranitrométhane; son spectre I.R. ne présente aucune des bandes caractéristiques du mésylate de départ; on le chromatographie sur alumine (12 g). L'éther de pétrole élue 353 mg de produit cristallisé A; l'éther de pétrole-éther 1:1 élue 25 mg de produit cristallisé, identifié par point de fusion, point de fusion de mélange et spectre I.R. avec le 3 β, 17 α-diacétate (VIII, R = R′ = Ac).

Le produit A donne un test positif au tétranitrométhane; il est recristallisé dans CH_2Cl_2—MeOH et sublimé. C'est un mélange d'oléfines, probablement *3 β-acétoxy octanor-dammara*-13(17) et -16-*ènes* (IX, R = Ac): $F = 146$–$150°$; $[\alpha]_j = +7°$ ($c = 1$; Chf.).

$C_{24}H_{38}O_2$ (358,54)	Calc. %	C: 80,35	H: 10,68
	Trouvé	C: 80,32	H: 10,69

Démésylation de l'acétate-mésylate (V, R = Ac, R′ = Més)

On chauffe à 80° pendant 1 heure une solution de 200 mg de l'acétate-mésylate dans 1 ml de lutidine fraichement distillée (conditions insuffisamment brutales!). On ajoute de l'eau, on filtre, lave à l'acide chlorhydrique dilué, puis à l'eau, on sèche

et on chromatographie le produit sur alumine (3,5 g). L'éther de pétrole élue une fraction présentant un test positif au tétranitrométhane (50 mg), qui est sublimée. C'est sans doute le *3β-acétoxy octanor-dammara-16-ène* (IX, R = Ac, double-liaison en 16,17): $F = 153$–$153{,}5°$.

$C_{24}H_{38}O_2$ (358,54)	Calc. %	C:	80,35	H:	10,68
	Trouvé	C:	80,50	H:	10,78

Equilibration de l'acétoxy-cétone (VII, R = Ac)

On dissout 400 mg de l'acétoxy-cétone (VII, R = Ac) dans 100 ml de benzène, et on agite magnétiquement pendant 12 heures avec 30 g d'alumine alcaline.[5] On filtre sur 5 g d'alumine en colonne, et on lave abondamment au benzène. Le produit élué est réacétylé (Ac_2O—Py) et recristallisé dans l'acétate d'éthyle. On obtient 192 mg de produit, $F = 182$–$187°$ (Pyrex), $[\alpha]_j -38°$ ($c = 1{,}1$; Chf.).

La chromatographie sur alumine neutre (20 g) donne, à l'éther de pétrole, 25 mg de cristaux homogènes, $F = 237$–$238°$ (Kof.), suivis de fractions à point de fusion plus étalé. Après recristallisation (CH_2Cl_2—AcOEt), on obtient le *3β-acétoxy 17-oxo octanor-(13α)-dammarane* (X, R = Ac): $F = 240°$ (Kof.); $[\alpha]_j -50°$ ($c = 0{,}8$; Chf.).

$C_{24}H_{38}O_3$ (374,53)	Calc. %	C:	76,96	H:	10,23
	Trouvé	C:	76,81	H:	10,36

Spectre I.R.: ν(C = O): 1725 cm^{-1} (acétate, *cyclo*pentanone) (Chf.).

Notes ajoutées à la correction des épreuves: (1) Les configurations absolues attribuées ici aux deux cétones isomères (VII) et (X) par la méthode des différences de rotation moléculaire ont été depuis confirmées par l'étude de leur dispersion rotatoire:

17-oxo 3β-acétoxy octanor-dammarane: D.R. ($c = 0{,}11$; MeOH): $[\alpha]_{700} +56°$; $[\alpha]_{589} +105°$; $[\alpha]_{315} +2390°$; $[\alpha]_{300} -714°$. Effet Cotton positif.

17-oxo 3β-acétoxy octanor-(13α)dammarane: D.R. ($c = 0{,}1$; MeOH): $[\alpha]_{700} +11°$; $[\alpha]_{589} -31°$ $[\alpha]_{310} -1664°$; $[\alpha]_{275} +1350°$. Effet Cotton négatif.

(2) De nouveaux essais d'équilibration des cétones (VII) et (X) semblent indiquer que la proportion de l'isomère *trans* (VII) *à* l'équilibre est encore beaucoup plus grande que nous ne l'indiquons ici. Cet équilibre est actuellement en cours d'étude.

[5] J. Castell et G. A. Fletscher, *J. Chem. Soc.* 3245 (1956).

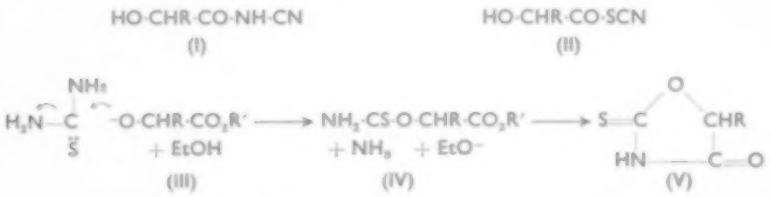
Tetrahedron, 1958, Vol. 3, pp. 310–316. Pergamon Press Ltd., London

NOTES

Acyl thiocyanates: on the nature of Clemmensen and Heitman's "Glycollyl and lactyl thiocyanates"

(*Received* 16 *October* 1957)

CLEMMENSEN and Heitman[1] found that interaction of ethyl glycollate or lactate with thiourea in refluxing ethanolic sodium ethoxide afforded, in addition to the expected acyl cyanamides (I; R = H and Me), small amounts of byproducts, which they concluded were acyl thiocyanates (II; R = H and Me). From our experience with acyl *iso*thiocyanates,[2] we suspected that the proposed structures were erroneous. Repetition of Clemmensen and Heitman's experiments revealed that ammonia was liberated, and we therefore inferred that the side-reactions comprised nucleophilic attack by the ethoxycarbonylalkoxide ions (III; R = H and Me, R′ = Et) on the carbon atom of thiourea followed by cyclisation of the intermediate *O*-thiocarbamoyl-glycollic or -lactic esters (IV; R = H and Me, R′ = Et) to the 2-thioöxazolid-4-ones (V; R = H and Me). Ahlqvist[3] found that the acid (IV; R = R′ = H) cyclised similarly on prolonged heating. Our thesis was confirmed, since the byproducts which we isolated had melting points which corresponded to those quoted by Clemmensen and Heitman, and were identical with authentic samples of the 2-thioöxazolid-4-ones.[4]



So far as we are aware, diphenylcarbamoyl thiocyanate[5] is the only acyl thiocyanate whose structure has been adequately established. It is possible that it owes its existence to the steric retardation of thermal isomerisation to the acyl *iso*thiocyanate, which is generally the more stable structure. It is noteworthy that the infra-red spectrum of diphenylcarbamoyl thiocyanate has a weak, sharp band at 2161 cm^{-1} similar to the spectra of alkyl thiocyanates and differing from the intense, broad bands in the spectra of alkyl *iso*thiocyanates and benzoyl *iso*thiocyanate.[6]

EXPERIMENTAL

2-Thioöxazolid-4-one. A mixture of ethyl glycollate (10·4 g) and thiourea (9 g) in a solution of sodium (2 g) in ethanol (100 cm^3) was heated under reflux for 2 hr. The solution was evaporated, diluted with water (100 cm^3), brought to pH 5 with acetic acid, and continuously extracted overnight with ether. The extract was evaporated, and the residue was purified by counter-current distribution between ether and water. The product (0·41g) was located by paper chromatography in butan-1-ol saturated with water (R_F 0·56), and isolated by evaporation. Recrystallised from water, it had m.p.

[1] E. Clemmensen and A. H. C. Heitman, *Amer. Chem. J.* **42,** 319 (1909).
[2] D. T. Elmore, J. R. Ogle, W. Fletcher and P. A. Toseland, *J. Chem. Soc.* 4458 (1956); D. T. Elmore and J. R. Ogle, *Proc. Chem. Soc.* 289 (1957); *J. Chem. Soc.* 1141 (1958).
[3] A. Ahlqvist, *J. Prakt. Chem.* **99,** 45 (1919).
[4] J. S. H. Davies, W. H. Hook and F. Long, *J. Chem. Soc.* 36 (1950).
[5] T. B. Johnson and L. H. Levy, *Amer. Chem. J.* **38,** 456 (1907).
[6] D. T. Elmore, Unpublished results.

110–111° and in admixture with an authentic sample;[4] the two specimens had identical infra-red spectra.

5-Methyl-2-thioöxazolid-4-one. The reaction was carried out exactly as described by Clemmensen and Heitman.[1] After removal of lactyl cyanamide, the mother-liquors were continuously extracted overnight with ether. The extract was evaporated and the residue was extracted with benzene-ether. The resultant extract was filtered and evaporated, and the residue (1·86 g) crystallised at 0°. Recrystallised twice from benzene-light petroleum (b.p. 40–60°) and twice from water, it had m.p. 91·0–91·5° and in admixture with an authentic specimen.[4] Comparison of infra-red spectra confirmed their identity.

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The rearrangement of scopinone to *m*-hydroxybenzaldehyde

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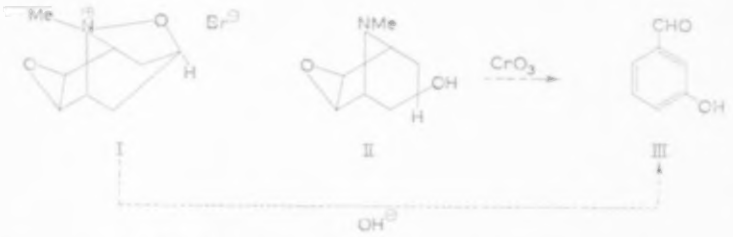
Recent studies of the elimination reactions of a variety of tropinone derivatives have shown that these reactions usually follow a normal course, giving rise to the expected troponoid products.[1] In this context, the early reports by Polonovski and Polonovski that the base degradation of scopinium bromide (I) and that chromic acid oxidation of *pseudo*scopine (II) both give a rearranged product, *m*-hydroxybenzaldehyde (III),[2] were of special interest. In order to gain further insight into these



transformations, a study of the elimination reactions of scopinone (IV) and its methobromide (V) has been carried out.

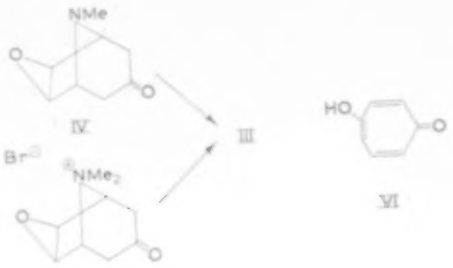
Scopinone was prepared for the first time by Heusner, as described in the adjoining Communication.[3] Scopinone methobromide (V) was found to suffer rapid degradation when treated with one equivalent of sodium bicarbonate at steam-bath temperatures. The chief organic product, formed in ca. 80 per cent yield, was found to be *m*-hydroxybenzaldehyde, identified both by spectral means and by isolation and comparison with an authentic sample of (III). Even in the absence of external base, (V) is converted into (III) after a short induction period. In this case it appears that the elimination is catalysed by the dimethylamine, which increases in concentration as the reaction progresses. Somewhat surprisingly, scopinone itself was found to undergo an analogous rearrangement, with or without added base, and even in the presence of acid. Thus, both elimination and rearrangement proceed with unprecedented ease in this series.

[1] J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, *J. Amer. Chem. Soc.* **77**, 4401 (1955); J. Meinwald and O. L. Chapman, *J. Amer. Chem. Soc.* **78**, 4816 (1956); E. E. van Tamelen, P. Barth and F. Lornitzo, *J. Amer. Chem. Soc.* **78**, 5442 (1956); J. Meinwald and O. L. Chapman, *J. Amer. Chem. Soc.* **80**, (1958).

[2] For leading references to these papers, see R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. I, pp. 302–307. Academic Press, New York (1950).

[3] A. Heusner and K. Zeile, *Tetrahedron* **3**, 313 (1958).

The possibility that (IV) or (V) are first converted to γ-tropolone (VI), which might then rearrange to (III) via a process consisting of a reverse aldol condensation followed by cyclization in a new



sense, has been excluded by an experiment in which (VI) was shown to be completely stable to prolonged base treatment.* We hope to publish a more detailed account of this work, as well as a discussion of its mechanistic implications, in the *Journal of the American Chemical Society*.

Acknowledgements—We are thankful to Dr. Alex Heusner for communicating his results before publication, as well as for providing a generous sample of scopinone methobromide. The partial support of this research by a Frederick Gardner Cottrell grant from the Research Corporation, New York, is gratefully acknowledged.

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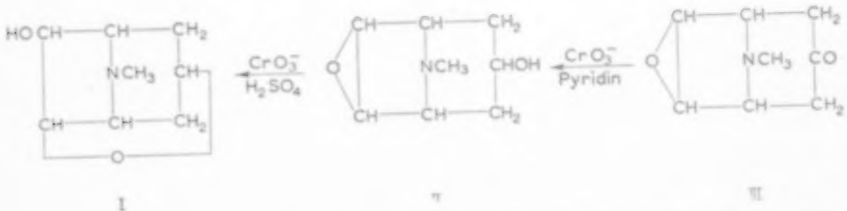
* A preliminary indication of the stability of γ-tropolone to base had already been provided by the work of T. Nozoe *et al.*[4]

[4] T. Nozoe, T. Mukai, Y. Ikegama and Toda, *Chem. & Ind.* 66 (1955).

Partialsynthese von Scopinon

(*Received* 17 *January* 1958)

Im Pyrrolidinring substituierte Derivate des Tropinons sind in letzter Zeit mehrfach als Ausgangsmaterialien für die Darstellung von Tropon und seinen Derivaten verwandt worden.[1] In diesem Zusammenhang teilen wir die Partialsynthese des bisher noch nicht bekannten Scopinons (6,7-Oxido-tropinon; III) mit. Versuche zur Totalsynthese von III hatten zu einer Ausweichreaktion



I II III

[1] J. Meinwald und O. L. Chapman, *J. Amer. Chem. Soc.* **78**, 4816 (1956), *Ibid.* **80**, 633 (1958); E. E. van Tamelen, B. Barth und F. Lornitzo, *Ibid.* **78**, 5442 (1956).

geführt,[2] während die Einwirkung von Chromtrioxyd in schwefelsaurer Lösung auf den entsprechenden Alkohol Scopin (II) lediglich Isomerisierung zu Scopolin (I) ergab.[3]

Wie wir fanden, lässt sich indessen II[3,4] durch das Chromtrioxyd-Pyridin-Reagens von Sarett und Mitarbeitern[5] mit Ausbeuten um 25% zu III oxydieren [Schmp. 65–67°, im I.R.-Spektrum ausgeprägte Carbonylbande bei 5·87 μ und zwei Oxiranbanden bei 11·62 und 11·88 μ, Pikrat Schmp. 175° (Zers.), Methobromid Schmp. 176° (Zers.)].

Über den Hofmannschen Abbau von III-Methobromid berichten Meinwald und Chapman in der nachstehenden Mitteilung.[6] Die ausführliche Beschreibung unserer Versuche wird in den *Chemischen Berichten* erfolgen.

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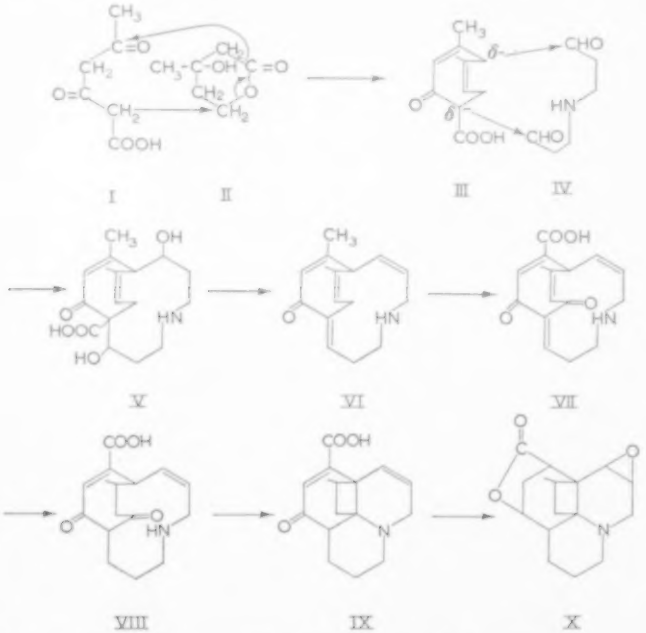
[2] Cl. Schöpf und A. Schmetterling, *Z. Angew. Chem.* **64**, 591 (1952); J. C. Sheehan und B. M. Bloom, *J. Amer. Chem. Soc.* **74**, 3825 (1952).
[3] R. Willstätter und E. Berner, *Ber. Dtsch. Chem. Ges.* **56**, 1079 (1923).
[4] J. Meinwald und O. L. Chapman, *J. Amer. Chem. Soc.* **79**, 605 (1957).
[5] G. I. Poos, G. E. Arth, R. E. Beyler und L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).
[6] J. Meinwald und O. L. Chapman, *Tetrahedron* **3**, 311 (1958).

The biogenesis of annotinine

(*Received* 28 *February* 1958)

Recently, the structure of annotinine (X) proposed by Wiesner *et al.*[1] has been confirmed by a striking three-dimensional analysis of annotinine bromohydrin.[2] The following biogenetic scheme is proposed for this interesting molecule.



[1] K. Wiesner, W. A. Ayer, L. R. Fowler and Z. Valenta, *Chem. & Ind.* 564 (1957).
[2] M. Przybylska and L. Marion, *Canad. J. Chem.* **35**, 1075 (1957).

Initial condensation is postulated between β,δ-diketocaproic acid (I) [derived from three acetate units] and mevalonic lactone (II) [a key intermediate in cholesterol[3] and terpene[4,5,6] biosynthesis], decarboxylation and dehydration leading to (III). Nitrogen is introduced into the molecule by the condensation of (III) with the dialdehyde amine (IV). This amine, or its biological equivalent, can be derived from two molecules of aspartic acid by conventional metabolic steps. It is of interest to note that Robinson[8] has proposed that the higher homologue of (IV) is a precursor of the pyrrolizidine alkaloids. Decarboxylation and dehydration of (V) yields compound (VI), which is oxidized at the allylic carbons to give (VII). Partial reduction results in the formation of (VIII), which undergoes an intramolecular Mannich reaction to give (IX), which contains the *cyclo*butane ring. Final steps are uneventful, involving reduction of the α,β-unsaturated ketone, lactonization and epoxidation of the double bond.

It is our intention to test this hypothesis by using radioactive tracers.

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[3] P. A. Tavormina, M. H. Gibbs and J. W. Huff, *J. Amer. Chem. Soc.* **78**, 4498 (1956).
[4] A. J. Birch, R. J. English, R. A. Massey-Westropp and H. Smith, *J. Chem. Soc.* 369 (1958).
[5] G. D. Braithwaite and T. W. Goodwin, *Biochem. J.* **67**, 13P (1957).
[7] E. C. Grob, *Chimia* **11**, 338 (1957).
[8] R. Robinson, *The Structural Relations of Natural Products* p. 72. Clarendon Press, Oxford (1955).

The alkylation of pyrrolidine enamines

(*Received* 20 *February* 1958)

THE elegant use of pyrrolidine enamines (I, Ia) of ketones as active intermediates for their C-alkylation and C-acylation has been described by Stork *et al.*,[1] the form (Ia) being that involved in reaction:

I Ia

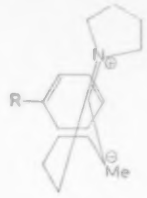
It was observed that monosubstitution only occurred (cf. Stork and Landesman[2]), for example, with *cyclo*hexanone and 5-phthalimido-2-tetralonepyrrolidine enamines, and the enamine of 2-methyl-*cyclo*hexanone was not C-methylated with methyl iodide.

That this monosubstitution may be a combination of steric effects due to the presence of the pyrrolidine ring and the α-alkyl substitution, which in the cases of the α-methylated *cyclo*hexanone (II) and 5-phthalimido-2-tetralone (III)-pyrrolidine enamines prevents the entry of a second methyl can be seen from measurements on Barton models[3] of (II) and (III, R = phthalimido). These give values of ca. 1 and 1·4 Å, respectively, for the distances between the α-hydrogen atoms of the pyrrolidine ring and the nearest hydrogen atoms of the α-methyl groups when these are equatorial. These are comparable to the "interference radii" of two hydrogen atoms (1·5 Å) of Crombie.[4] Hence the methyl groups must take up the axial conformation in the active forms (II) and (III) so that equatorial substitution is blocked by the pyrrolidine ring, and in the case of (II) axial substitution in the 6-position is also blocked by the axial methyl group. Were the α-methyl groups to remain equatorial in (II) and (III), the coplanarity of the four bonds from the $C{=}\overset{\oplus}{N}$ group [a necessary condition[5] for the existence of the forms (II) and (III)] would be prevented, and hence C-alkylation again inhibited. In

[1] G. Stork, R. Terrell and J. Szmuszkovicz, *J. Amer. Chem. Soc.* **76**, 2029 (1954).
[2] G. Stork and M. K. Landesman, *J. Amer. Chem. Soc.* **78**, 5128 (1956).
[3] D. H. R. Barton, *Chem. & Ind.* 1136 (1956).
[4] Cf. E. A. Braude and F. Sondheimer, *J. Chem. Soc.* 3754 (1955).
[5] M. J. S. Dewar, *Electronic Theory of Organic Chemistry* Chap. I. Oxford University Press (1948).

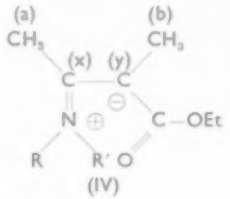
cases in which C-alkylation proceeds by rearrangement of N-alkylated forms (cf. Stork and Landesman[5]), arguments involving the stereochemistry of form (Ia) naturally do not apply.

II



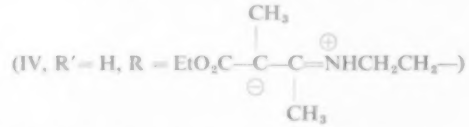
III

The difficulty encountered in di-C-alkylating acetoacetic ester enamines[6] is germane to this topic, as steric grounds here might perhaps be thought to be excluded. In considering a model of the active monomethylated form (IV) two assumptions arise: (*i*) the carbonyl oxygen is attracted towards the positively charged nitrogen so that the ester group is *cis* to the $C{=}\overset{\oplus}{N}$ group (taken to be 1·3 Å long) and almost in the same plane, (*ii*) the C_x—C_y bond has partial double bond character with a length of 1·39 Å (cf. benzene). Since the methyl groups (*a*) and (*b*) will be as far apart as possible, measurements on models show that an entering methyl must take up a position where its nearest hydrogen



(IV)

atoms are ca. 1·45 Å from those of CH_3(*a*). Therefore as before the entry of a second methyl group is hindered. It should be noted that ethylene bis-*β*-amino-α-methylcrotonate



can be C-methylated,[6] and unidentified side-products are also formed; here repulsion between the ester groups may oppose the stereochemistry invoked in assumption (*i*).

The formation of pyrrolidine enamines probably proceeds[7] through the form (Ia), so that the ease of formation of a given pyrrolidine enamine should depend on the amount of hindrance to form (Ia) present in a given ketone. In connection with this it was found that neither α-tetralone nor 5-hydroxy-6:8-dimethyl-1-tetralone (V) reacted with pyrrolidine in benzene [76 and 85 per cent recovery of α-tetralone (identified as semicarbazone) and (V), respectively]. The Barton models show very strong interference between the 8-methyl group of (V)-pyrrolidine enamine and the pyrrolidine ring, while the distance between the 8-hydrogen atom of α-tetralonepyrrolidine enamine and the α-hydrogen atoms of the pyrrolidine ring is 1·64 Å.

Acknowledgements—I am indebted to Drs. F. M. Dean and D. A. H. Taylor for discussions of this topic.

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[6] R. Robinson, *J. Chem. Soc.* **109**, 1038 (1916).
[7] J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *J. Amer. Chem. Soc.* **78**, 430 (1956).

Reaction of phloroglucinol with sodium borohydride

(*Received* 3 *March* 1958)

PHLOROGLUCINOL, on treatment with an excess of sodium borohydride in aqueous solution, is converted into resorcinol. The reaction presumably occurs by initial reduction of the phloroglucinol to the dihydro compound, followed by dehydration.

Catechol, resorcinol, quinol, pyrogallol, and β-naphthol were unchanged after similar treatment with sodium borohydride.

EXPERIMENTAL

A solution of phloroglucinol dihydrate (2·3 g) in water (100 ml) was added during 30 min to a stirred solution of sodium borohydride (3·1 g) in water (20 ml). The stirring was continued for a further 1½ hr, and then the excess of sodium borohydride was decomposed by the cautious addition of dilute hydrochloric acid. The resulting aqueous solution was evaporated under reduced pressure, and the residue was extracted with benzene in a Soxhlet apparatus for 12 hr to give, after evaporation of the solvent, crude resorcinol (1·4 g, 90 per cent), m.p. 100–107°; recrystallisation from benzene afforded a pure specimen, m.p. and mixed m.p. 109–110°. The dibenzoate had m.p. 117–117·5°, undepressed on admixture with an authentic specimen.

In similar experiments with catechol, resorcinol, quinol, pyrogallol and β-naphthol, the starting materials were recovered in 80–90 per cent yields. The experiment with β-naphthol was carried out at the reflux temperature.

Acknowledgement—I thank Sir Robert Robinson, O.M., F.R.S., for his interest.

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Tetrahedron, 1958, Vol. 3, pp 317–321. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATIONS

Sulfoxides as nucleophiles*

(*Received* 15 *March* 1958)

We wish to record the novel and interesting behavior of dimethylsulfoxide (DMSO) as a nucleophilic ionizing solvent for reactions with alkyl halides or arenesulfonates (RX). Judging ionizing power from relative rates of acid production from *p*-methoxyneophyl toluenesulfonate,[1] which is disposed toward anchimerically[2] assisted ionization, dimethylsulfoxide falls below the common solvolysing solvents, acetic acid and ethanol[3] (Table 1). On the other hand, it displays greater ionizing power than such solvents as dimethylformamide and dry acetone. The relatively high nucleophilicity of dimethylsulfoxide is evident from the solvent sequence observed with other substrates, such as 1,1-diphenyl-2-propyl *p*-bromobenzenesulfonate[4] and ethyl *p*-toluenesulfonate[5]

TABLE 1. SOLVENT RATE SEQUENCE IN SOLVOLYSIS OF SEVERAL ARENESULFONATES

Compound	Relative rates				
	AcOH	EtOH	Me_2SO	$HCONMe_2$	Me_2CO
p-Methoxyneophyl OTs, 75°	9·23[1]	3·42[1]	(1·00)	0·27	0·0468
1,1-Diphenyl-2-propyl OBs, 75°	1·02[4]	0·491[4]	(1·00)	0·084	0·0055
Ethyl OTs, 50°	0·00158[5]	0·101[5]	(1·00)		

(Table 1). With these materials, rates of reaction in DMSO are substantially greater than in ethanol. The tendency for nucleophilic solvent participation by DMSO in the rate-determining step of the reaction of RX molecules, is further evident from the structural rate sequence,[3,5] Me, 3 > Et, 1 < Pr^i, 1·5, for the alkyl toluenesulfonates in DMSO at 50°.

The action of DMSO on simple RX molecules gives rise to two different types of derivatives, both with the proper elementary analysis for 1:1 adducts of RX and DMSO (Table 2). O-alkyl derivatives (I) are obtained conveniently in yields of 50–90 per cent by isolation of the product of reaction of methyl, ethyl or benzyl arenesulfonates in DMSO at the proper stage. By the use of methyl iodide and silver nitrate in DMSO, the O-methyl nitrate is derived. More stable isomeric S-alkyl adducts of DMSO(II) may also be obtained. This type of derivative is derived from benzyl toluenesulfonate in DMSO after long reaction periods. With methyl iodide, the S-alkyl product is the only one which we have been able to isolate. Treatment of this derivative with silver arenesulfonate or silver nitrate in water gives rise to the S-alkyl arenesulfonate or nitrate (Table 2).

In water or aqueous ethanol the O-alkyl adducts hydrolyse rapidly to produce one equivalent of acid (Table 2), while the S-alkyl derivatives are quite inert. In fact, they may be recrystallized from water. The O-alkyl derivatives tend to isomerize in solution to the S-alkyl variety, the tendency for

* Research supported by the National Science Foundation.

[1] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.* **78,** 2763 (1956); S. Winstein and R. Heck, *J. Amer. Chem. Soc.* **78,** 4801 (1956); A. H. Fainberg, Unpublished work.
[2] S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *J. Amer. Chem. Soc.* **75,** 147 (1953).
[3] S. Winstein, E. Grunwald and H. W. Jones, *J. Amer. Chem. Soc.* **73,** 2700 (1951).
[4] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *J. Amer. Chem. Soc.* **74,** 1113 (1952.)
[5] S. Winstein and H. Marshall, *J. Amer. Chem. Soc.* **74,** 1120 (1952).

such isomerization decreasing in the order of anions, $I^{\ominus} > \overset{\ominus}{O}NO_2 > \overset{\ominus}{O}Ts$. While other mechanisms may also be possible, the available data suggest than an important route from O- to S-alkyl derivatives involves reversibility of formation of the O-alkyl adduct and competing formation of the S-alkyl derivative. During reaction of 0·037 M methyl iodide in DMSO at 50°, the O → S conversion is so important that only 7 per cent of acid-producing O-adduct, formed rapidly, can be detected kinetically. In contrast, 94 per cent of O-adduct can be detected with 0·030 M methyl *p*-bromobenzenesulfonate in DMSO at 50°.

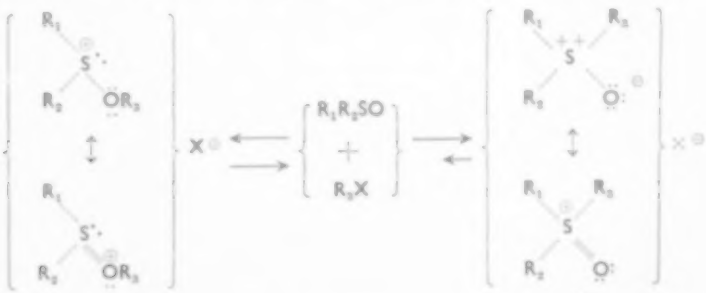
TABLE 2. SUMMARY OF SULFOXIDE ALKYLATION PRODUCTS

R_1R_2SO	R_3X	O-alkyl derivatives		S-alkyl derivatives m.p. (°C)
		m.p. (°C)	Acid* (per cent)	
$(CH_3)_2SO$	CH_3I	—	—	220†
	CH_3ONO_2	66–68	92·4	220·0–220·5
	CH_3OTs	48–54	95·0	165–167
	CH_3OBs	98–99	98·2	232–233
	C_2H_5OTs	83–89	97·6	—
	$C_6H_5CH_2OTs$	92–93‡	97·5	119·5–120
$C_6H_5CH_2SOCH_3$	CH_3OTs	79–80‡	98·0	

* Percentage of one equivalent of acid by titration of an aqueous solution to the phenolphthalein end-point.
† Depends upon rate of heating.
‡ Mixed m.p. 72–74°.

The present observations indicate that the O- and S-alkylation products (I) and (II) are associated with kinetic and thermodynamic control of products, respectively, with the range of RX molecules so far explored. The only other report of similar alkylation of DMSO of which we are aware is the very recent one of Kuhn's,[6] which appeared after the present work was essentially complete. Kuhn and Trischmann[6] made the important observation that methyl iodide reacts in DMSO solution and have isolated a methiodide and several other derivatives prepared by metathetical reactions of the methiodide. Because methyl iodide was the only RX molecule investigated and the methiodi de was inevitably the S-alkyl variety, the duality of possible alkylation products was not observed.

The identification of the O- and S-alkyl derivatives (I) and (II) is clear from both physical and chemical evidence. The proton magnetic resonance (NMR) absorption spectrum of the O-adduct of DMSO and methyl *p*-bromobenzenesulfonate in chloroform displays three peaks in addition to the single solvent peak. The areas of these peaks in the order of increasing shielding are in the ratio



R. Kuhn, *Angew. Chem.* **17**, 570 (1957); R. Kuhn and H. Trischmann, *Liebigs Ann.* **611**, 117 (1958).

4 : 3 : 6. These correspond to the aromatic, O-methyl and S-methyl protons, respectively, of the O-methyl derivative(I). The NMR spectrum of a fresh solution of the S-adduct of DMSO and methyl nitrate in deuterium oxide shows only one type of proton, corresponding to the S-methyl derivative(II).

The comparison of the initial adducts from DMSO and benzyl *p*-toluenesulfonate, on the one hand, and benzylmethylsulfoxide, methyl iodide and silver *p*-toluenesulfonate, on the other, supplies further evidence regarding the O- or S-alkyl nature of the adducts from kinetic control of products. The two adducts containing the benzyl group differ in melting point (Table 2) as well as in behavior in hydrolysis. Benzyl alcohol is obtained from the DMSO–benzyl toluenesulfonate product, and methanol is derived from the benzylmethylsulfoxide–methyl toluenesulfonate adduct. Since the two adducts would be identical if S-alkylation were involved, the chemical evidence agrees with the NMR results in favor of the O-alkyl designation (I) for the adducts from kinetic control of products.*

The dialkyl-alkoxysulfonium and trialkyl-oxosulfonium salts (I) and (II) represent interesting new materials. For example, they may be of some interest as alkylating agents. Further, the trimethyl-oxosulfonium nitrate (II; $R_1 = R_2 = R_3 = CH_3$; $X^{\ominus} = \overset{\ominus}{NO_3}$) undergoes very rapid exchange of deuterium for protium even in neutral deuterium oxide solution. The rate of this exchange may be estimated from the change in the NMR spectrum of the solution with time, since the C–H absorption disappears and an O–H absorption appears as exchange proceeds. In this way, a rough first-order rate constant of ca. 6×10^{-4} sec^{-1} was estimated for the exchange at room temperature (ca. 28°). The exchange in this case is faster by a factor of ca. 20 than that observed by Doering and Hoffmann[7] with trimethylsulfonium iodide at 26·8° in deuterium oxide, 0·2615 M in sodium deuteroxide. One could anticipate powerful acceleration of deuterium exchange by the addition of an oxygen atom to trimethylsulfonium ion, and the available facts make it clear that the oxygen substituent in the trimethyl-oxosulfonium derivative (II) accelerates deuterium exchange by at least several powers of ten.

The new sulfoxide derivatives, especially the O-alkyl variety (I), may play important roles as intermediates in other reactions occurring in DMSO or other sulfoxide solvents. Possible examples are the relatively efficient olefin formation from many alkyl arenesulfonates in DMSO as solvent[8] or the conversion of phenacyl bromides to phenylglyoxals in DMSO reported recently by Kornblum.[9]

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* The S-methyl designation (II) for the thermodynamically favored adduct turns out to be in agreement with Kuhn and Trischmann's[6] structural assignment to the DMSO methiodide on the basis of their treatment of the methiodide with hot concentrated hydriodic acid, a reaction of questionable validity for proof of structure.

[7] W. von E. Doering and A. H. Hoffmann, *J. Amer. Chem. Soc.* **77**, 521 (1955).
[8] S. Smith and J. Takahashi, Unpublished work.
[9] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Amer. Chem. Soc.* **79**, 6562 (1957).

Optical rotatory dispersion studies—XVIII*

Demonstration of conformational mobility in 2-chloro-5-methyl*cyclo*hexanone†

(*Received* 28 *March* 1958)

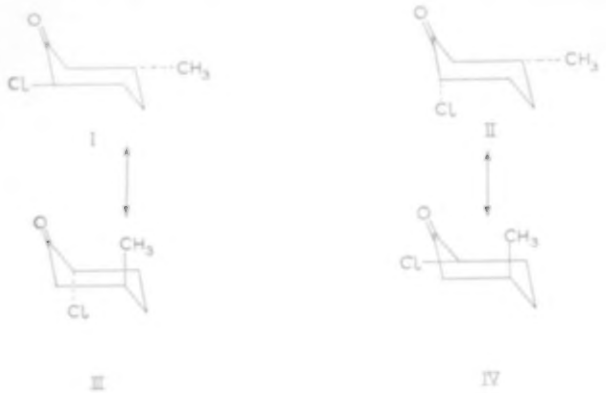
ON the basis of extensive rotatory dispersion measurements of halogenated steroid ketones,[1] an empirical rule has been proposed,[2] which states that the sign of the single Cotton-effect curve[3] of the parent *cyclo*hexanone is not altered by introduction of equatorial bromine or chlorine in the α or α′ positions, but that axial halogen can invert the sign in a predictable manner. Since all earlier work[1]

* Paper XVII, C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *J. Amer. Chem. Soc.* In press.
† Supported by grant No. CY-2919 of the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.
[1] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **80** (1958).
[2] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* **79**, 1506 (1957).
[3] For nomenclature, see C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957).

has been carried out with polycyclic systems of rigid conformation, it was of considerable interest to extend such observations to monocyclic *cyclo*hexanones.

Chlorination of (+)-3-methyl*cyclo*hexanone with sulfuryl chloride in carbon tetrachloride gave 2-chloro-5-methyl*cyclo*hexanone (m.p. 68–69°, $[\alpha]_D$ +6·4° ($CHCl_3$). (*Anal.* Found for $C_7H_{11}OCl$: C, 56·97; H, 7·71; O, 11·07; Cl, 23·80 per cent,) which was dehydrochlorinated with 2,4-dinitrophenylhydrazine to give optically active 5-methyl-2-*cyclo*hexen-1-one 2,4-di-nitrophenylhydrazone (m.p. 143–145°, $[\alpha]_D$ −211° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 380 mμ. *Anal.* Found for $C_{13}H_{12}O_4N_4$: C, 53·79; H, 4·83; N, 19·31 per cent).

Two pairs of conformational isomers are possible for the chloroketone, one of them *trans* (I, III) and the other (II, IV) *cis*. Ultraviolet and infrared measurements* indicate—in agreement with expectation[4]—that the amount of axial isomer predominates in a non-polar medium (octane) and is reduced in a polar solvent (methanol). The spectral measurements do not, however, distinguish



between the two possible axial (II *or* III) or the two equatorial (I *or* IV) conformers and a unique solution to this problem can be secured by optical rotatory dispersion measurements.

According to our earlier empirical rule,[2] (I), (II) and (IV) should have a positive Cotton effect[3] curve—as does the starting ketone (+)-3-methyl*cyclo*hexanone[5,6] itself—while only conformer (III) should exhibit a negative curve. Since the spectral measurements* indicate a preponderance of the axial form in octane, the rotatory dispersion of 2-chloro-5-methyl*cyclo*hexanone was first measured in octane solution and found to exhibit a strong, single negative Cotton-effect curve[3] (trough at $[\alpha]_{330}$ −1092°), from which it follows that conformer (III) rather than (II) represents correctly the axial form of the chloroketone. Most strikingly, when the dispersion curve was measured in methanol solution, where the spectral data* indicate a considerable amount of the equatorial isomer, it proved to be positive (peak at $[\alpha]_{295}$ +626°).†

This dramatic inversion of the sign of the Cotton-effect curve on changing from a non-polar to a polar solvent can best be rationalized by assuming that in the former solvent the *cyclo*hexanone exists to a large extent as (III) and in the polar medium as the "flipped-over" conformer (I). The energy difference between (I) and (III) is rather small—the "3-alky ketone" effect[7] in (III) roughly counterbalancing the unfavorable electrostatic effect of the equatorial chlorine atom in (I), thus allowing for the polarity of the solvent[4] to be the decisive factor.

Further work with optically active halogenated *cyclo*hexanones is in progress, but it is pertinent

* Details will be published in our complete paper.

† That no isomerization of axial to equatorial chlorine in the same conformer (*trans* (III) to *cis* (IV)) had occurred was demonstrated by dissolving the substance in methanol, evaporating (after 45 min) to dryness *in vacuo* and quickly measuring the dispersion in octane (starting with the characteristic trough in the 330 mμ region), which again proved to be negative.

[4] J. Allinger and N. L. Allinger, *Tetrahedron* **2**, 64 (1958). Extensive personal discussion with these authors is gratefully acknowledged.

[5] H. S. French and M. Naps, *J. Amer. Chem. Soc.* **58**, 2303 (1936).

[6] C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957).

[7] W. Klyne, *Experientia* **12**, 119 (1956).

to point out at this time that this represents still another example of the great utility of the rotatory dispersion technique[6] in the examination of conformational problems.[6]

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[6] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* In press; see also Paper XVII, C. Djerassi *et al.*

Kinetics of a nucleophilic replacement of an aromatic nitro group

(*Received* 18 *April* 1958)

SODIUM methoxide reacts with 1:4-dinitronaphthalene in methanol solution to give only the nitrite ion and 4-nitro-1-naphthyl methyl ether. The reaction may be followed by sampling at convenient intervals into toluene and water, with subsequent absorptiometric determination of the nitrite ion in the aqueous phase by a diazotisation–coupling process as described by Rider and Mellon.[1]

The kinetics are of second order, viz.:

$$\text{rate} = k[\text{methoxide}]\,[1{:}4\text{-dinitronaphthalene}]$$

and salt effects appear to be absent. The Arrhenius parameters have been calculated from determinations of the specific rate at six temperatures and are:

Activation energy = 19·2 kcal/g mole
Frequency factor ($\log_{10} A$) = 11·4

It is interesting to compare these values with those for *p*-dinitrobenzene, given by Bolto and Miller[2] as 22·4 kcal/g mole and 12·6, respectively.

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[1] B. F. Rider and M. G. Mellon, *Industr. Engng. Chem. (Anal.)* **18,** 96 (1946).
[2] B. A. Bolto and J. Miller, *Aust. J. Chem.* **9,** 74 (1956).

1-Methoxyvinyl esters*

(*Received* 21 *May* 1958)

WE have found that mercuric salts catalyse the addition of carboxylic acids to methoxyacetylene (I) in methylene chloride solution, the reaction constituting the first general method for the preparation of 1-methoxyvinyl esters† (II). The following examples illustrate the marked catalytic effect of mercuric ions in the formation of II. Whereas the uncatalysed addition of acetic acid (1 mole) to I (2 moles) gave only 25 per cent of IIa (the remainder being anhydride), the addition of 2 mole per cent of mercuric acetate (based on acid) gave 95 per cent IIa. Previous attempts to prepare the analogous 1-ethoxyvinyl acetate have been reported as unsuccessful.[6] In the case of *p*-phenylazobenzoic acid, negligible reaction occurred when a suspension of 1 mole in methylene chloride was

* Contribution No. 1501 from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut.

† Until recently,[1–5] 1-alkoxyvinyl esters were not described in the literature.

[1] G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Amer. Chem. Soc.* **76,** 1715, 1720 (1954).
[2] R. Broekema, S. van der Werf and J. F. Arens, *Rec. Trav. Chim.* **77,** 258 (1958).
[3] J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.* **23,** 635 (1958).
[4] A. S. Kende, *Chem. and Ind.* 1053 (1956).
[5] F. D. Cramer and K. G. Gärtner, *Chem. and Ind.* 560 (1958).
[6] J. F. Arens and P. Modderman, *Proc. Koninkl. Nederland. Akad. Wetenschap.* **53,** 1163 (1950); *Chem. Abstr.* **45,** 6152*d* (1951); G. Eglinton, E. R. H. Jones, B. L. Shaw and M. C. Whiting, *J. Chem. Soc.* 1862 (1954).

stirred for 12 hr with 2·5 moles of I. However, with the addition of 0·5 and 5 mole per cent of mercuric acetate (based on acid), the reaction was complete in 9, and 1·5 hr respectively, and negligible amounts of anhydride were formed. The 1-methoxyvinyl esters prepared by this general method are recorded in the accompanying table. They all exhibit a sharp band at ca. 5·95 μ in the infrared which is as intense as that due to the ester carbonyl.

The activity of the esters (II) as acylating agents is exemplified by the reaction of a slight excess of IIa with benzylamine (vigorously exothermic); β-naphthylamine (2 hr at 80°); 2,4-dinitrophenol (8 hr at room temperature); and *p*-nitrobenzyl alcohol (3 hr at 80°). After removal of any volatiles,

TABLE I

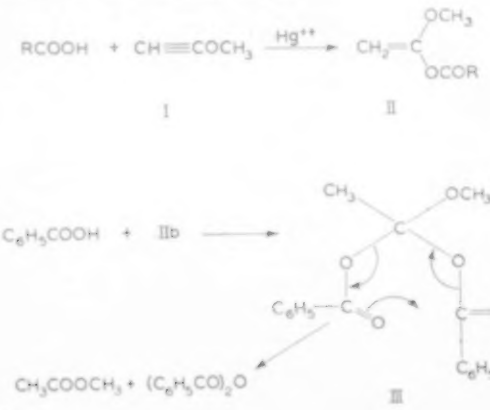
R	II	Yield (%)*	b.p. or m.p.	Calcd.			Found		
				C,	H,	N or Cl	C,	H,	N or Cl
CH_3	a	75	79° (85 mm)	51·7	6·9		51·8	6·8	
C_6H_5	b	98	95–96° (0·5 mm)	67·4	5·7		67·7	5·8	
p-$NO_2C_6H_4$	c	66	76·5–78°	53·8	4·1	6·3	53·7	4·3	6·4
3,5-$(NO_2)_2C_6H_3$	d	98	93·5–95·5°	44·8	3·0	10·4	45·0	3·2	10·3
p-$C_6H_5N{=}NC_6H_4$	e	80	93·5–94·5°	68·1	5·0	9·9	68·0	5·1	9·9
$(C_6H_5)_2CCl$	f	71	63–63·5°	67·4	5·0	11·7	67·5	4·9	11·5
†	g	85	136·5–137·5°	72·9	9·1		73·3	9·1	

* Although the yields of the crude esters were almost quantitative, some loss resulted in the removal of small amounts of contaminating anhydride.

† IIg = 1-methoxyvinyl 3β-acetoxy- Δ^5-bisnorcholenate.

nearly quantitative yields of the acetyl derivatives were obtained. The use of the esters (II) as intermediates in the synthesis of peptides offers attractive possibilities.[3,5]

Compounds corresponding to II have been postulated as intermediates in the useful conversion of an acid to its anhydride by I.[6] Indeed, the reaction of acetic acid and benzoic acid with IIa and IIb respectively, gave nearly quantitative yields of the corresponding anhydrides. This conversion undoubtedly occurs by intermediate formation of III, followed by subsequent decomposition to anhydride via a cyclic transition state, rather than by direct attack of acid at the carbonyl carbon atom of II, as the following results show. When 1 mole of IIb was treated with 1 mole of benzoic acid containing 1·06 at. per cent excess ^{18}O per oxygen, benzoic anhydride containing 0·53 at. per cent excess ^{18}O per oxygen was recovered and the methyl acetate concurrently formed was found to contain 0·52 at. per cent excess ^{18}O in the carbonyl oxygen.



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Tetrahedron, 1958, Vol. 3, pp. 323–324. Pergamon Press Ltd., London

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Paper Symposium on Aromatic Character

INTRODUCTION

by Sir ROBERT ROBINSON

THE designation "aromatic" was first applied to a group of natural products such as methyl salicylate (oil of wintergreen), anethole, (aniseed), safrole (sassafras), coumarin (Touka bean), and vanillin, etc., on account of their characteristic odours or flavours. When it was recognised that many of these substances were derivatives of benzene the classification acquired a structural significance and the "aromatic" series implied "benzene and its derivatives".

The scope of the definition was enlarged to include "polycyclic nuclei such as naphthalene, anthracene and phenanthrene" and a consideration of the essential common characters of these substances led to the extension to pyridine and its family and also to thiophene with furane and pyrrole by analogy.

At this stage the common "aromatic" molecular quality was sought and found in the possession of a stable nucleus which is readily formed and has a strong tendency to remain unchanged in chemical reactions. One illustration of this is the occurrence of substitution rather than addition reactions.

The next phase was the attempt to generalise the structural relations in the enlarged aromatic series in terms of valency theory, inevitably in the later stages on an electronic basis and finally with the help of the two usual wave-mechanical treatments.

This has certainly led to a deeper, more satisfying, understanding of the nature of "aromatic" compounds in the wider sense but all the logical implications are not yet generally acceptable. There remains a contribution from the older systematics and this is approved by most organic chemists as a matter of convenience.

To take one example, the theoretical requirements for "aromaticity" are found in the carboxylion, $R{\cdot}CO_2^-$, because this is a stable group with a tendency to retain its type and there exists an electronic system, the formation of which is associated with a diminution of free energy. This may be crudely illustrated by the symbols:

(— = 2e, or ⁝)

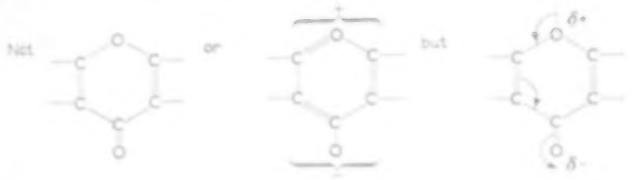
When the writer (with J. W. Armit in 1926) proposed the term "aromatic sextet" to denote a group of six electrons which by their presence and wave-mechanical interactions conferred a special stability on the molecular structure, the existence of similar groups such as that in the carboxylions was recognised. The "aromatic sextet" itself has proved a fertile conception, and it supplied an immediate explanation

of such phenomena as the aromaticity of pyridine salts (the unshared electrons of the nitrogen atom not being involved in the sextet), the aromaticity of thiophene and pyrrole, and the stability of the anions derived from *cyclo*pentadiene derivatives.

benzenoid sextet
sextet without use of unshared 2e in nitrogen
using 2e lone pair in S
using 2e left on CH after ionisation

Many more complex applications of the sextet have since been proposed, and among the more interesting are those in which electron transfer from one ring of a fused system to another is facilitated by the development of aromaticity in one or both nuclei.

In the anhydronium bases there is a similar compromise in the effects of opposing forces, neutralisation of electrical charges and tendency to aromaticity.



This was the first example to be proposed of hybridisation by conjugative electron displacement starting from a "classical" structure. The concept was by no means confined to γ-pyrones and especially the amides represent an even simpler case of hybridisation. The mis-called "resonance" theory, after an uneasy initial dynamic period, is now generally interpreted in the more static terms of hybrid molecules. It is hardly likely that an agreed definition of aromaticity will be evident in the papers of this Symposium, and it is hoped that discussion may ensue and reduce the area of disagreement, at least in the use of words. The present interest in the field is centred on more exact calculation on the one hand, and the discovery of new aromatic types on the other. It is hoped further contributions of an original nature will enable the theme to be developed in a significant manner in this Journal.

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THE SIGNIFICANCE OF KEKULÉ STRUCTURES FOR THE STABILITY OF AROMATIC SYSTEMS

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(*Received* 1 *October* 1957)

Abstract—The attempted synthesis of the hydrocarbons (I), (XXII) and (XXIX) with no Kekulé structures indicates that these hydrocarbons are unstable diradicals that polymerise immediately. Quantum mechanics can not offer a stable arrangement of paired electrons in molecular orbitals in cases where Kekulé structures fail. Perinaphthene (X) and perinaphthone (XIII) show a pronounced tendency to go over into ring systems with an aromatic frame work of alternating double bonds with an odd electron or a positive charge in the centre. Tribenzoperinaphthene (XVI) is oxidised in acid solution with molecular oxygen to salts of the type (XVII), which are not paramagnetic. Combinations of two perinaphthyl radicals, (XVIII) or (XXI), go over either into the stable red hydrocarbon zethrene (XIX) with two fixed double bonds in the centre or into the diradical with no Kekulé structure (XXII). The newly described synthesis of the next higher benzologue (XIX) with no Kekulé structure indicates that the latter is an unstable diradical. All the experimental results support the view that Kekulé structures are of paramount importance for the stability of aromatic systems.

QUANTUM mechanics characterises the aromatic state by the distribution of paired electrons in molecular orbitals (MO) which extend over the whole ring system. This method does not need Kekulé structures. Therefore it would be of considerable interest to synthesise hydrocarbons with no Kekulé structure which might be possibly described by a MO structure. A hydrocarbon of this kind is the symmetric triangulene $C_{22}H_{12}$, which has an even number of carbon and hydrogen atoms. From the standpoint of classical chemistry this hydrocarbon has no Kekulé structure and can be only formulated as a diradical like (I).

From the standpoint of quantum mechanics the structure (II) with the frame of alternating double bonds might be considered a possibility in which the four electrons in the centre could be arranged in pairs in MO's. The recently synthesised methylene-*cyclo*propene (III)[1] shows that such a system is reasonably stable. It should be even more stable when included in an aromatic system like (II), provided Kekulé structures were not essential for the aromatic state. In that case resonance might occur between the three structures as indicated in (III). The synthesis of the colourless hexahydrotriangulene (IV) was carried out by Clar and Stewart.[2] When this hydrocarbon was dehydrogenated by methods that succeeded in the preparation of even the most reactive aromatic hydrocarbons like hexacene, the fundamental hydrocarbon triangulene polymerised immediately and could not be observed even for a short time.

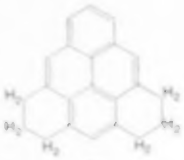
It is obvious that triangulene reacts as a diradical (I). Longuet-Higgins[3] came to the same results by quantum mechanical calculations. This view is further supported by the course of the reduction of the red, stable, triangulenequinone (VI). This gives a deep bluish-green vat with alkaline sodium dithionate solution. That seems to

[1] J. T. Cragson, K. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Amer Chem. Soc.* **75**, 3344 (1953).
[2] E. Clar and D. G. Stewart, *J. Amer. Chem. Soc.* **75**, 2667 (1953); **76**, 3504 (1954).
[3] H. C. Longuet-Higgins, *J. Chem. Phys.* **18**, 265 (1950).

I

II

III



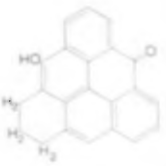
IV

V

VI

VII

VIII



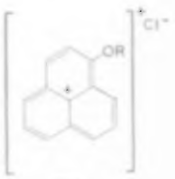
IX

X

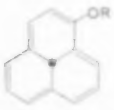
XI

XII

XIII



XIV



XV

XVI

XVII

indicate that the vat was derived from the diradical dihydroxytriangulene (VII). However, it forms only a monosodium salt and must have therefore the structure (VIII). Further reduction gives (IX) and not a derivative of dihydrotriangulene (V), which is a yellow easily oxidisable hydrocarbon. It shares its sensitivity to oxygen with perinaphthene (X).

There is increasing evidence that perinaphthene (X) and perinaphthone (XIII) tend to go over into compounds with a frame of alternating double bonds and an odd electron or a positive charge in the centre.[4] Thus perinaphthene (X) is oxidised in the air to perinaphthone (XIII) via the radical perinaphthyl (XI), whose existence can be proved by paramagnetic measurements[5] and whose lifetime extends over months. The radical formula (XI) has only two Kekulé structures, whilst (XII) has eighteen Kekulé structures. A radical of the type (XII) should have a very short lifetime like the radicals phenyl or naphthyl. The centrosymmetric formula (XI) is therefore a better expression for its stability. This casts some doubt on the current assumption of the equal contribution of Kekulé structures. It is obvious that the two structures (XI) if not the only ones, are strongly preferred.

Perinaphthone (XIII) shows also a strong tendency to form a cyclic polyenic frame. It dissolves in hydrochloric acid to give a yellow salt (XIV) (R = H).[6] It also adds acid chlorides to form (XIV) (R = acetyl or benzoyl), from which the chlorine can be removed with Grignard magnesium. The blue solution probably contains the radical (XV).[7] The preparation of the radical (XI) and one of its trimethyl derivatives has been described by Reid[8] recently. When perinaphthone (XIII) is reduced in alkaline dithionate solution, a red intermediate stage is observed before the pale yellow dihydro stage is reached. In fact, potentiometric measurements indicate the formation of a radical monohydro stage.[9]

The tendency to form a centrosymmetric system is so strongly pronounced that tribenzoperinaphthene (XVI) is oxidised in acetic acid solution by atmospheric oxygen to a blue salt (XVII) (X = CH_3CO_2). Although the blue acetate is not very stable, the corresponding chloride and perchlorate are stable crystalline compounds.[10] These salts are not paramagnetic and show no paramagnetic resonance absorptions.* They have therefore the non-radical structure (XVII).

If two perinaphthyl radicals are combined, the two dibenzotetracenes (XVIII) and (XXI) are formed. If the possibilities of Kekulé structures for the two molecules are disregarded, the two odd electrons could be paired and both should be nonradical non-paramagnetic aromatic hydrocarbons. The centrosymmetric dibenzotetracene (XIX), which was given the name "zethrene"[11] because of its Z-shape, has a similar spectrum to 1:2-7:8-dibenzoperylene.[12] The spectrum is not related to any spectrum of the diarylpolyene type. Therefore it must be concluded that zethrene is a normal aromatic hydrocarbon in spite of the two fixed double bonds in the central region.

* These measurements were kindly carried out by Prof. J. Weiss and Dr. P. A. Forrester in Newcastle.

[4] E. Clar, *Aromatische Kohlenwasserstoffe* p. 431. Springer-Verlag (1952).
[5] P. B. Sogo, M. A. Nakazaki and M. Calvin, *J. Chem. Phys.* **26**, 1343 (1957).
[6] E. Bamberger and M. Philip, *Liebigs Ann.* **240**, 147 (1887).
[7] E. Clar and D. G. Stewart, see E. Clar.[4]
[8] D. R. Reid, *Chem. & Ind.* 1504 (1956).
[9] P. Beckmann and H. Silerman, *Chem. & Ind.* 1635 (1955).
[10] E. Clar and D. G. Stewart, *J. Chem. Soc.* **23**, (1958).
[11] E. Clar, K. F. Lang and H. Schulz-Kiesow, *Chem. Ber.* **88**, 1520 (1955).
[12] E. Clar, *Chem. Ber.* **82**, 46 (1949).

Moreover, it shows the same annellation effect as perylene. Thus the long-wave absorption bands shift to the violet when passing from zethrene to 4:5-11:12-dibenzozethrene (XX) (Fig. 1) exactly as in passing from perylene to 2:3-8:9-dibenzoperylene.[13] The fixed double bonds in the centre of the two zethrenes do not alter the aromatic character to any appreciable extent.

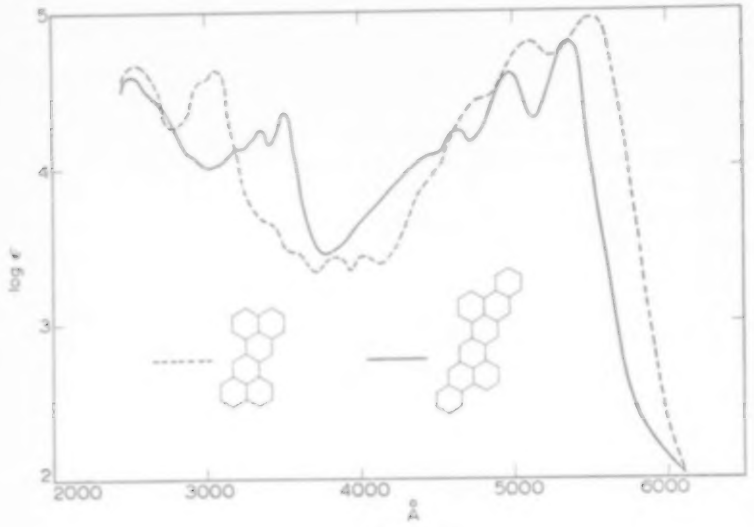
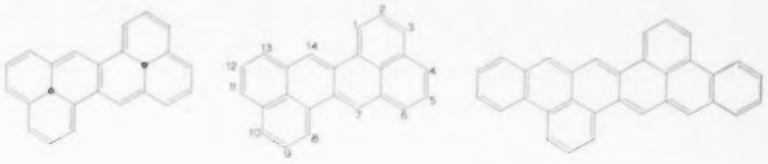


FIG. 1.
(———) 4:5-7:8-Dibenzozethrene (XX). E. Clar and H. Schulz-Kiesow, unpublished results. Absorption maxima (Å) and log ε (in parenthesis): 5350 (4·80), 4975 (4·60), 4650 (4·25), 3525 (4·36), 3360 (4·25) in trichlorobenzene, 2540 (4·58) in dioxan. (- - - -) Zethrene (XIX), see Clar *et al.*

Contrary to this result 1:12-10:11-dibenzotetracene (XXII) does not seem to be a stable aromatic hydrocarbon. Its attempted synthesis is described in this paper for the first time. It begins with the di-(1-dinaphthyl) carbinol[13] (XXIV), which after transformation into the chloride was condensed with magnesio-malonic ester. The dinaphthyl malonic ester (XXV) was so obtained in good yield and in a simpler way than recently described by Newman and Lednicer.[14] Unexpectedly the ring closure to (XXIII) proved extremely difficult, owing to the fact that (XXV) tends to split into naphthalene and perinaphthone when the standard methods are applied. Only phosphorus pentoxide in boiling nitrobenzene gave a very small yield of the orange quinone (XXIII). Since it does not give a vat with alkaline dithionate solution, this quinone does not seem to be a true quinone but rather a diketone. The amount of (XXIII) available was not enough to carry on with the synthesis of dibenzotetracene (XXII).

The prospects of synthesising dibenzopentacene (XXIX) seemed more promising than the synthesis of dibenzotetracene (XXII) and would serve the same purpose of testing the possibilities for the preparation of a similar hydrocarbon with no Kekulé structure. The diketone (XXVI) was obtained from dichloro*iso*phthaloyl dichloride,

[13] J. Schmidlin and P. Massini, *Ber. Dtsch. Chem.Ges.* **42**, 2377 (1909).
[14] M. S. Newman and D. Lednicer, *J. Amer. Chem. Soc.* **78**, 4765 (1956).



XVIII XIX XX

XXI XXII XXIII

XXIV XXV

XXVI XXVII

XXVIII XXIX

naphthalene and aluminium chloride. Ring closure to (XXVII) was effected by potassium hydroxide in boiling quinoline under carefully controlled conditions. The quinone (XXVII) tends to split with excess of potassium hydroxide into a dicarboxylic acid.

The quinone or rather diketone (XXVII) also forms no vat like (XXIII) and can

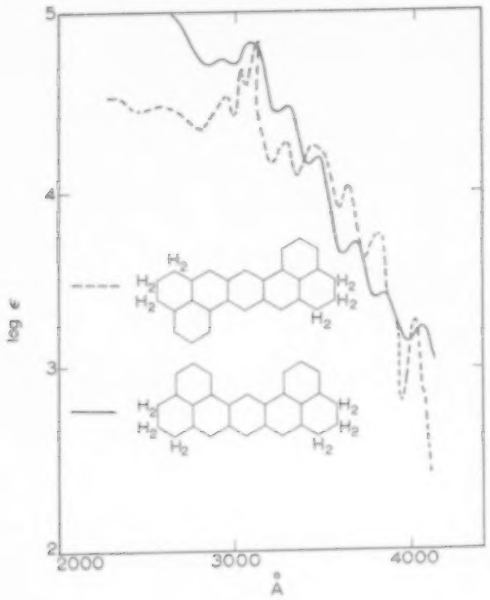


FIG. 2.
(———) 1:14-11:12-Dibenzo 2:3:4:8:9:10-hexahydro-pentacene (XXVIII) in alcohol. Absorption maxima (Å) and log ε (in parentheses): 4050 (3·27), 3860 (3·41), 3660 (3·70), 3460 (4·18), 3300 (4·48), 3090 (4·84), 2940 (4·75). (– – – –) 4:5:6:12:13:14-Hexahydroheptazethrene in alcohol, see Clar[1] (p. 394).

be reduced to the hexahydro compound (XXVIII) by hydroiodic acid and red phosphorus. This hydrocarbon has a similar absorption as its centrosymmetric isomer hexahydroheptazethrene, as shown by the comparison in Fig. 2. As in the case of hexahydrotriangulene (IV), this hexahydro derivative (XXVIII) was dehydrogenated with palladium charcoal under conditions suitable for the preparation of the most sensitive aromatic hydrocarbons. Here again the dehydrogenation and complete polymerisation took place simultaneously. It must be therefore concluded that 1:14-11:12-dibenzopentacene (XXIX) is an unstable diradical. The unsuccessful attempts to prepare aromatic hydrocarbons with no Kekulé structure support the view that Kekulé structures are of paramount importance for the stablity of aromatic ring systems.

EXPERIMENTAL*

Di-(1-*naphthyl*)*methylmalonic acid* (XXV)

Di-(1-naphthyl)chloromethane (30 g) in 400 ml of dry benzene was added to a solution of magnesio-malonic ester in benzene (200 ml), which was prepared according to the method of Lund[15] from 7·5 g of magnesium.

* Melting points are uncorrected and were taken in evacuated capillaries.

[1] H. Lund, *Ber. Dtsch. Chem. Ges.* **67**, 935 (1934).

The mixture was heated under reflux for 30 hr and then cooled, and excess of magnesio-malonic ester was destroyed by shaking with 500 ml of dilute sulphuric acid. The benzene solution was then shaken with dilute sodium carbonate solution, washed with water and dried over magnesium sulphate; the benzene was distilled off to leave a semi-crystalline mass, which consisted mainly of di-(1-naphthyl)methyl-malonic ester. Recrystallisation from ethanol gave ivory needles, m.p. 113° (Newman and Lednicer[14] give 113–114·2°) (Found: C, 78·77; H, 5·76. $C_{28}H_{26}O_4$ requires C, 78·85; H, 6·15 per cent).

The crude ester was then hydrolysed by boiling for 6 hr with 500 ml of 15% alcoholic potassium hydroxide solution, after which most of the alcohol was removed by distillation. Then 400 ml of water was added and the remainder of the alcohol was distilled off azeotropically. The resulting aqueous solution was diluted to 1 l., filtered, cooled and acidified with concentrated hydrochloric acid, thus precipitating white needles of the required dicarboxylic acid (XXV), which was then filtered off, washed with water and dried. Yield, 32 g or 84 per cent of theoretical.

The acid was recrystallised from glacial acetic acid, as white needles, m.p. 238°, containing one molecule of water of crystallisation (Found: C, 74·30; H, 5·35. $C_{24}H_{18}O_4.H_2O$ requires C, 74·21; H, 5·19 per cent).

The dicarboxylic acid dissolved slowly in concentrated sulphuric acid to give a bluish-green solution, which on warming to 80° became yellow and at 100° changed to red.

The attempted cyclisation of di-(1-*naphthyl*)*methylmalonic acid* (XXV)

(*a*) Liquid hydrogen fluoride did not alter the acid within 24 hr.

(*b*) Polyphosphoric acid did not achieve ring closure at 100°. At 170° cyclisation and partial splitting occurred. The only product isolated by recrystallisation from benzene and light petroleum was a small amount of perinaphthone, m.p. 142°, identified by mixed melting point with an authentic sample.

(*c*) A melt of the acid with sodium chloride and aluminium chloride at 160° for 3 min yielded a dark condensation product, which was mostly insoluble in benzene and could not be purified by chromatography. A similar result was obtained when zinc dust was added to the melt.

(*d*) A cyclisation and reduction with 55% hydriodic acid and red phosphorus in a sealed tube at 200° for 4 hr gave a solid material, which after extraction with ether and washing of the extract with water and sodium carbonate, was distilled at 10^{-2} mm. The first fraction consisted of colourless crystals with the characteristic odour of naphthalene. The following oily fraction, which did not crystallise, was dehydrogenated with palladium–charcoal. A sticky yellow solid distilled off the catalyst, which showed the characteristic absorption bands at 4440 and 4160 Å (in benzene) of peropyrene. Peropyrene is a condensation product obtained by reduction of perinaphthone.[16]

(*e*) A dark-green insoluble solid was obtained when the acid (XXV) was first transformed into the chloride and then treated with aluminium chloride in nitrobenzene. When benzene was used as a solvent, a small amount of perinaphthone was isolated.

(*f*) The cyclisation of the acid (XXV) with boiling benzoyl chloride and a few drops of sulphuric acid in nitrobenzene gave an insoluble dark condensation product.

[16] E. Clar, *Ber. Dtsch. Chem. Ges.* **76**, 458 (1943).

1:12-10:11-*Dibenzotetracene*-4:5-*quinone* (XXIII)

The dicarboxylic acid (XXV) (5 g) was dissolved in nitrobenzene (50 ml) at 130° and phosphorus pentoxide (15 g) was added with stirring. The colour of the solution changed to green, then violet and then brown within 10 min. The mixture was treated with water (100 ml) and the nitrobenzene was removed by steam-distillation. The dark residue was filtered off, boiled with dilute ammonia solution, filtered off and dried (4·1 g). Recrystallisation from xylene gave red-brown needles, m.p. 270–280° (dec.) (Found: C, 86·8; H, 3·7. $C_{24}H_{12}O_2$ requires C, 86·7; H, 3·6 per cent). The quinone dissolved in concentrated sulphuric acid to give a red-violet solution; it also dissolved in concentrated hydrochloric acid to give a similar red-violet solution.

The above-described procedure sometimes yielded an isomeric compound without any apparent reason. This compound had m.p. 270–280° (dec.) and dissolved in concentrated sulphuric acid to give a green solution but it did not dissolve in concentrated hydrochloric acid (Found: C, 87·0; H, 4·1. $C_{24}H_{12}O_2$ requires C, 86·7; H, 3·6 per cent). It gave no vat with alkaline sodium dithionate.

1:3-*Dichloro*-4:6-*di*-(-*naphthoyl*)*benzene* (XXVI)

The acid chloride (from 50 g of 4:6-dichloro*iso*phthalic acid[17] treated with 90 g of phosphorus pentachloride) was dissolved in methylene dichloride (150 ml) with naphthalene (55 g), and anhydrous aluminium chloride (60 g) was added over 1½ hr. During the vigorous reaction the solution changed from brown to red. The mixture was shaken overnight, poured into ice and hydrochloric acid, and the solvent and excess of naphthalene were removed by steam-distillation, to leave a brown oil, which solidified on cooling and could be ground in a mortar (58 g of crude product).

A sample was recrystallised from benzene–ethanol–water (2:4:1) as white needles, m.p. 157° (Found: C, 73·92; H, 3·69; Cl, 15·74. $C_{28}H_{16}O_2Cl_2$ requires C, 73·86; H, 3·54; Cl, 15·57 per cent).

The colour in concentrated sulphuric acid was orange and, on heating, yellow.

1:14-11:12-*Dibenzopentacene*-5:7-*quinone* (XXVII)

(a) *With potassium hydroxide in quinoline.* The crude diketone (XXVI) (10 g) was heated under reflux in quinoline (50 ml) with potassium hydroxide pellets (2·5 g) for 8 hr and then poured into dilute hydrochloric acid (400 ml). The aqueous liquors were decanted off, and the tarry mass was boiled with water (300 ml) and then with dilute ammonia solution (300 ml), the aqueous solutions again being removed by decantation. On cooling, the dark tar solidified and was ground in a mortar with ethanol (10 ml). Yield (crude) 8·5 g.

Chromatography on alumina, with benzene and chloroform (1:1) as eluant, gave brown needles, which were sublimed twice at 300° and 10^{-2} mm pressure. This gave orange needles of the *quinone* (XXVII), softening at 280°, m.p. 342° (Found: C, 87·83, H, 3·87. $C_{28}H_{14}O_2$ requires C, 87·94; H, 3·69 per cent). The colour in concentrated sulphuric acid was red, with very faint orange fluorescence. It did not form a vat in alkaline sodium dithionate solution.

(*b*) *With potassium hydroxide in alcohol.* Strong alcoholic potassium hydroxide solution was prepared by evaporation of a 10% solution till the boiling point rose to 140°.

[17] A. Claus and H. Burstert, *J. Prakt. Chem.* **41**, 552 (1890).

The diketone (XXVI) (5 g) was added to this and heated for ½ min at 140°. The mixture was cooled and poured into water. The insoluble material (0·5 g of crude) was the quinone (XXVII) and could be washed with water and purified as described above under (*a*). The alkaline solution was acidified with hydrochloric acid and the resulting white solid was filtered off and recrystallised twice from aqueous acetic acid (1:1). White needles of a *dinaphthylbenzenedicarboxylic acid*, m.p. 153° (Found: C, 76·74; H, 4·85·$C_{28}H_{18}O_4.H_2O$ requires C, 77·05; H, 4·62 per cent). The colour in concentrated sulphuric acid was violet, fading rapidly to brown and, on heating becoming pale red.

1:14-11:12-*Dibenzo*-2:3:4:8:9:10-*hexahydropentacene* (XXVIII)

The quinone (XXVII) (1g) was ground with red phosphorus (0·34 g) and added to constant-boiling hydriodic acid (10 ml) in a large sealed tube. This was heated at 200° for 8 hr. The contents were extracted with benzene, and the benzene solution well washed with water and sodium dithionate solution and dried. Chromatography on alumina, with light petroleum (boiling range 60–80°) containing 30 per cent of benzene as eluant, gave yellow needles of the *hexahydro derivative* (XXVIII), softening at 197°, m.p. 215° (Found: C, 93·85; H, 6·23. $C_{28}H_{22}$ requires C, 93·81; H, 6·19 per cent). In concentrated sulphuric acid it dissolved very slowly to give a brown-green solution with red fluorescence, which, on heating, became olive green with red fluorescence.

Dehydrogenation of 1:14-11:12-*dibenzo*-2:3:4:8:9:10-*hexahydropentacene* (XXVIII)

The hexahydro derivative (XXVIII) (30 mg) was sublimed in a current of air-free carbon dioxide into the palladised charcoal catalyst at 310° and 10^{-3} mm pressure, but was completely absorbed in it. The temperature was raised to 500°, but no sublimate was obtained from the catalyst.

The efficiency of the catalyst was tested both before and after this experiment by the dehydrogenation of 9:10-dihydroganthracene to anthracene in good yield.

The complete testing of the catalyst and dehydrogenation of the hexahydro derivative (XXVIII) was repeated several times with identical results.

Acknowledgements—Microanalyses by Mr. J. M. L. Cameron and Miss M. W. Christie, Glasgow University.

Tetrahedron, 1958, Vol. 3, pp. 334–338. Pergamon Press Ltd., London

THE PREPARATION OF SOME PYRIDINIUM *CYCLO*PENTADIENYLIDES

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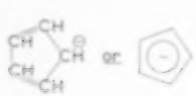
United College of St. Salvator and St. Leonard, University of St. Andrews

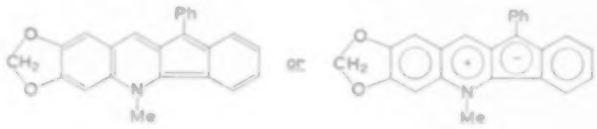
(*Received* 4 *November* 1957)

Abstract—The preparation of some pyridinium *cyclo*pentadienylides is described. A brief survey of earlier work in this field is included.

THE formation of the negatively charged *cyclo*pentadienide ring (I) was first recognised by Thiele[1] in 1901, when he prepared potassium *cyclo*pentadienide. Armit and Robinson,[2] in studies on anhydronium bases such as (II), pointed out that the pentagonal carbocyclic ring in these compounds would be stabilised by the sharing of a lone pair of electrons from the pyridine nitrogen atom, as it would thereby achieve an "aromatic sextet" of electrons. Goss and Ingold[3] similarly connected the acidity of *cyclo*pentadiene and its derivatives with the aromatic sextet of electrons realised in its negative ion.



(I)



(II)

The negatively charged *cyclo*pentadienide ring could be achieved not only by anion formation, but also in a dipolar molecule such as (III), and Ingold and Jessop[4] ascribed a structure of this type (IV) to the purple-coloured transitory intermediate obtained in the degradation of fluorene-9-trimethylammonium salts with alkali. Later, they isolated and described a more stable sulphonium analogue (V).[5] Investigations[6] of the dipole moment of (IV) and (V) confirmed their highly polar character.

(III)
(VIII), X = N_2

(IV), X = NMe_3
(V), X = SMe_2
(VI), X = N_2
(VII), X = O_2

[1] J. Thiele, *Ber. Dtsch. Chem. Ges.* **34**, 68 (1901).
[2] J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).
[3] F. R. Goss and C. K. Ingold, *J. Chem. Soc.* 1268 (1928).
[4] C. K. Ingold and J. A. Jessop, *J. Chem. Soc.* 2357 (1929).
[5] C. K. Ingold and J. A. Jessop, *J. Chem. Soc.* 713 (1930).
[6] G. M. Phillips, J. S. Hunter and L. E. Sutton, *J. Chem. Soc.* 146 (1945); H. Hartmann and H. Grossel, *Z. Elektrochem.* **61**, 337 (1957).

Since Ingold and Jessop's work, the preparation of other fluorenylides has been described by a number of workers.[6–9] Most of these compounds are unstable, but those derived from nitrofluorenes[7] have markedly greater stability. Other compounds, not specified as ylides in the literature, but which have probably at least a measure of ylide structure, include the red crystalline diazofluorene (VI)[10] and fluorenone peroxide (VII).[11]

The first compound to be described with an ylide structure (III) derived from *cyclo*pentadiene itself was diazo*cyclo*pentadiene (VIII),[12] prepared by Doering and DePuy in 1953, although it is possible that other unstable compounds of this type had been prepared.[13] Subsequently the preparation of a number of *cyclo*pentadienylides with *exo*cyclic ammonium[14–16] or phosphonium[17] groups has been reported.

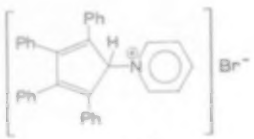
(IX) (X) (XI)

Pyridinium *cyclo*pentadienylide (IX)[14] was prepared by the action of two molecules of pyridine on one molecule of dibromo*cyclo*pentene, followed by treatment with alkali. This ylide separated out as a red-brown crystalline precipitate, which when freshly prepared has a coppery lustre. On exposure to air, and especially in direct light, it tarnishes slowly, apparently owing to oxidation, but samples stored *in vacuo* or under nitrogen appear unchanged after 18 months. If the solution obtained by treatment of the dibromo*cyclo*pentene with pyridine is kept for some time before treatment with alkali, the resultant ylide appears to be rather more stable than when this intermediate is basified at once. The most striking property of this ylide is the intensity and diversity of the colours of its solutions. The shade varies with the polarity of the solvent, ranging from colourless in acidic aqueous solution, through orange in alcohols, red in acetone, chloroform and methylene dichloride to a reddish-purple in ether, benzene, pyridine and ethylaniline, and a blueish-purple in light petroleum. Kosower,[18] discussing charge-transfer spectra, has commented that such a range of

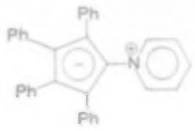
[7] E. D. Hughes and K. I. Kuriyan, *J. Chem. Soc.* 1609 (1935); A. Novelli and A. P. G. de Varela *Ciencia e Invest.* 82 (1948); *Chem. Abstr.* **42**, 5912 (1948).
[8] F. Krollpfeiffer and K. Schneider, *Liebigs Ann.* **530**, 34 (1937); L. A. Pinck and G. E. Hilbert, *J. Amer. Chem. Soc.* **60**, 494 (1938); *Ibid.* **68**, 751, 2011 (1946); G. Wittig and G. Felletschin *Liebigs Ann.* **555**, 133 (1944); G. Wittig, M. Heintzeler and M. H. Wetterling, *Liebigs Ann.* **557**, 201 (1947); G. Wittig, R. Mangold and G. Felletschin, *Liebigs Ann.* **560**, 116 (1948); G. Wittig, *Angew. Chem.* **63**, 15 (1951).
[9] F. Kröhnke, *Chem. Ber.* **83**, 253 (1950).
[10] M. Staudinger and O. Kupfer, *Ber. Dtsch. Chem. Ges.* **44**, 2197 (1911); M. Staudinger and A. Gaule, *Ber. Dtsch. Chem. Ges.* **49**, 1951 (1916); L. A. Pinck and G. E. Hilbert, *J. Amer. Chem. Soc.* **68**, 867 (1946).
[11] G. Wittig and G. Pieper, *Ber. Dtsch. Chem. Ges.* **73**, 295 (1940).
[12] W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.* **75**, 5955 (1953).
[13] See J. Thiele, *Ber. Dtsch. Chem. Ges.* **33**, 666 (1900); A. Eibner and O. Laue, *Ber. Dtsch. Chem. Ges.* **39**, 2022, (1906); A. Roedig and L. Hörnig, *Chem. Ber.* **88**, 2003 (1955); A. P. Terent'ev and L. L. Gomberg, *J. Gen. Chem.* (*U.S.S.R.*) **8**, 662 (1938); *Chem. Abstr.* **33**, 1285 (1939).
[14] D. Lloyd and J. S. Sneezum, *Chem. & Ind.* 1221 (1955).
[15] W. W. Spooncer, Dissertation, Univ. of Washington (1955); *Chem. Abstr.* **50**, 10664 (1956); and personal communication.
[16] D. N. Kursanov, N. K. Baranetskaia and V. N. Setkina, *Dokl. Akad. Nauk SSSR* **113**, 116 (1957).
[17] F. Ramirez and S. Levy, *J. Org. Chem.* **21**, 488, 1333 (1956); *J. Amer. Chem. Soc.* **79**, 67 (1957).
[18] E. M. Kosower and P. E. Klinedinst, *J. Amer. Chem. Soc.* **78**, 3493 (1956).

colours might be expected of a compound with this structure. The compound is only sparingly soluble in the non-polar solvents, but its solubility is rather greater in more polar ones; it dissolves in acid and is reprecipitated by alkali. On slow heating it decomposes before melting.

The structure of (IX) follows from its mode of preparation, its physical properties and its quantitative reduction to N-*cyclo*pentylpiperidine, identified by means of an oxalate and a picrate, which were shown to be identical (mixed m.p.) with authentic specimens.[19] It also appears to couple with benzenediazonium chloride (cf. Ramirez and Levy[17]) to give a product whose solutions are more intensely coloured than those of the original ylide, the chloroform and benzene solutions being red-purple and alcoholic solutions bright red.



(XIII)



(XIV)

Ylides were similarly obtained by the action of α-, β- and γ-picolines, 2:6-lutidine and 2:4:6-collidine on dibromo*cyclo*pentene.

It was thought possible that the intermediates firstly formed by the action of pyridine or its analogues on dibromo*cyclo*pentene, and which are transformed by caustic alkali into ylides, might have structures such as (X) or (XI)*; Ramirez and Levy[17] have already postulated the latter formulation. The former seemed unlikely in view of the stability of this intermediate; further, it gave a picrate (m.p. 192°) that was different from the picrate obtained from the ylide itself (dec. 95°). Elementary analysis of the picrate of the intermediate obtained from γ-picoline (and also from a similar compound obtained from dimethylsulphide and dibromo*cyclo*pentene) confirm this supposition.

Ylides derived from indene (cf. Kröhnke[9]) and from 2:3:4:5-tetraphenyl*cyclo*pentadiene have also been investigated. A different preparative route was used, the dienes being brominated with N-bromosuccinimide and the resultant bromo derivatives treated with pyridine or other base.

In the case of indene, the 1-bromoindene reacts with pyridine to give a deep-red solution, presumably of indene-1-pyridinium bromide, which, on treatment with caustic alkali, gives a dark-blue material, which can be extracted into chloroform. The blue coloration is very fugitive and the pyridinium indenylide thus resembles the corresponding fluorenylide in its instability. Both of these ylides are therefore less stable than the *cyclo*pentadiene derivatives; this may be due to the annellation of the benzene rings.[22]

When pyridine was added to 1-bromo-2:3:4:5 tetraphenyl*cyclo*pentadiene, after a short time a yellow precipitate began to form, which was filtered off after the mixture had been set aside for 24 hr. This proved to be N-(2:3:4:5-*tetraphenyl*cyclo*pentadienyl*)-*pyridiniumbromide* (XIII). It is insoluble in water, but on shaking it with water to

* Formula (XI) assumes 1:4-addition of bromine to *cyclo*pentadiene.[17,20,21]

[19] J. Loevenich, H. Utsch, P. Moldrickx and E. Schaefer, Jr., *Ber. Dtsch. Chem. Ges.* **62**, 3084 (1929).
[20] J. Thiele, *Liebigs Ann.* **314**, 296 (1900); E. H. Farmer and W. D. Scott, *J. Chem. Soc.* 172 (1929).
[21] W. G. Young, H. K. Hall, and S. Winstein, Jr., *J. Amer. Chem. Soc.* **78**, 4338 (1956).
[22] Cf. B. Pullman and G. Berthier, *Bull. Soc. Chim. Fr.* **15**, 551 (1948).

which a little alcohol has been added a deep blue-purple precipitate appears, whose formation is hastened by the addition of alkali. This precipitate is 1-pyridinium-2:3:4:5-tetraphenyl*cyclo*pentadienylide (XIV). It appears to be completely stable in the solid state, but decomposes in solution when exposed to air. As in the case of the unphenylated ylides the colour of the solutions depends on the solvent, in this case being red with alcohol and blue with benzene or ether.The ylide formed a picrate that was identical with that prepared from the intermediate (XIII). Corresponding ylides could be obtained by using β- or γ-picoline instead of pyridine, but α-picoline and 2:6-lutidine gave only small yields of such ylides, very possibly owing to steric hindrance in these cases. Quinoline and *iso*quinoline also gave ylides only in small yields, and they appeared to be less stable.

EXPERIMENTAL

Bromination of cyclo*pentadiene*.[20] *cyclo*Pentadiene (10 g) dissolved in chloroform (33 ml) was cooled in ice–salt, and bromine (23·5 g, 7·5 ml) in chloroform (30 ml) was added during 1 hr, the mixture being stirred meanwhile.

Pyridinium cyclo*pentadienylide* (IX). The solution of dibromo*cyclo*pentene was added to a solution of pyridine (26·5 g, 27 ml) in chloroform (20 ml) and set aside overnight. Chloroform was then distilled off at room temperature, the residue was extracted with water and the extract was made alkaline by addition of sodium hydroxide solution. A lustrous red-brown precipitate of *pyridinium* cyclo*pentadienylide* was formed (18·9 g, 87 per cent) (Found: C, 82·5; H, 6·8; N, 8·2. $C_{10}H_9N$ requires C, 83·9; H, 6·3; N, 9·8 per cent). Satisfactory analyses were difficult to obtain throughout this series of compounds, although analyses were conducted with special care. It seems likely that strenuous retention of water or uptake of atmospheric oxygen may be the cause of these errors. (IX) was only very sparingly soluble in non-polar solvents, but rather more soluble in polar solvents such as acetone, chloroform or methylenedichloride.

Hydrogenation of (IX). The ylide (IX) (0·5 g) was dissolved in ethanol and shaken with hydrogen over Adams's platinum oxide catalyst; 420 ml of hydrogen was rapidly taken up (including absorption by catalyst; calc. 390 ml). After filtration from the catalyst and removal of the ethanol, the residue was distilled and gave a main fraction, b.p. 83°/10 mm, of N-*cyclo*pentylpiperidine, which gave a *picrate*, m.p. 167–168°, after crystallisation from ethanol (Found: C, 50·2; H, 5·7; N, 14·3. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·8; N, 14·7 per cent), and an oxalate,[19] m.p. 181°, both of which were shown to be identical (mixed m.p.) with derivatives obtained from a genuine sample of N-*cyclo*pentylpiperidine, prepared as described by Loevenich *et al.*[19]

Reaction of other pyridine analogues with dibromo*cyclo*pentene*. To the base* (1 g) in a little chloroform was added an equivalent amount (0·5 mol. equiv.) of a solution of dibromo*cyclo*pentene in chloroform. The mixture was set aside for 1–2 days with occasional shaking. Chloroform was then distilled off at room temperature, and the residue was extracted with water and made alkaline. Any precipitate was filtered off or, alternatively, the alkaline solution was extracted with chloroform to obtain the ylide.

*Bis-γ-picolinio*cyclo*pentene salts* (XI, R = CH_3; see footnote, p. 336). Two

* α-, β- and γ-picoline, 2:6-lutidine and 2:4:6-collidine.

molecular equivalents of γ-picoline were added to a solution of dibromo*cyclo*pentene in chloroform. The solution was set aside overnight, chloroform was removed at room temperature, and then an ethanolic solution of picric acid was added to the residue in ethanol. The *picrate* of *bis-γ-picolinio*cyclo*pentene* separated and was crystallised from water, m.p. 223–225° (Found: C, 49·4; H, 3·2; N, 15·7. $C_{29}H_{24}O_{14}N_8$ requires C, 49·2; H, 3·4; N, 15·8 per cent). *Bis*(*dimethylsulphono*)cyclo*pentene dipicrate* m.p. 162–164° (XII) is similarly obtained from dibromo*cyclo*pentene and dimethyl sulphide (Found: C, 39·1; H, 3·0; N, 13·1; S, 9·9. $C_{21}H_{22}O_{14}N_6S_2$ requires C, 39·0; H, 3·4; N, 13·0; S, 9·9 per cent).

Pyridinium Indenylide. 1-Bromoindene, prepared by the action of N-bromosuccinimide on indene,[23] was treated with excess of pyridine. On addition of sodium hydroxide solution to the deep-red solution thus obtained, a dark-coloured deposit was formed, which was extracted into chloroform to give a blue solution. The colour faded in a few minutes.

Pyridinium 2:3:4:5-*tetraphenyl*cyclo*pentadienylide* (XIV) *and related homologues.* 1-Bromo-2:3:4:5-tetraphenyl*cyclo*pentadiene (1·0 g) was prepared by the method of Kainer[24] and set aside overnight with an excess (6 ml) of pyridine. The solution soon turned red and a yellow precipitate formed, which was filtered off, washed with *n*-hexane and recrystallised from ethanol. This proved to be N-(2:3:4:5-*tetraphenyl*-cyclo*pentadienyl*) *pyridinium bromide* (XIII), m.p. 213·5–215·5° (1·09 g, 93 per cent) (Found: N, 2·7; Br, 14·9; $C_{31}H_{26}NBr$ requires N, 2·7; Br, 15·1 per cent). (XIII) is insoluble in water, but, when shaken with water containing a little ethanol or acetone, it gives a dark-blue crystalline precipitate of *pyridinium*-2:3:4:5-*tetraphenyl*-cyclo*pentadienylide* (XIV), m.p. 208–210° (Yields averaged 87 per cent) (Found: C, 90·6; H, 5·6; N, 3·2. $C_{31}H_{25}N$ requires C, 91·3; H, 5·6; N, 3·1 per cent). The formation of (XIV) from (XIII) is hastened by the presence of sodium hydroxide. (XIV) is soluble in ethanol to give a red solution, and in benzene and ether to give blue solutions. It is stable to air as the solid, but not in solution; the colours of the solutions fade after a few hours' exposure. (XIV) forms a *picrate*, m.p. 226–228°, after crystallisation from ethanol (Found: C, 69·7; H, 4·7; N, 7·7. $C_{49}H_{28}N_4O_7 \cdot C_2H_5OH$ requires C, 69·8; H, 4·7; N, 7·8 per cent); an identical picrate (mixed m.p.) may be obtained from (XIII). γ-Picoline reacts similarly with 1-bromo-2:3:4:5-tetraphenyl*cyclo*pentadiene to give N-(2:3:4:5-*tetraphenyl*cyclo*pentadienyl*)-*γ-picolinium bromide* (XV), m.p. 218–220° (Yields average 76 per cent) (Found C, 77·2; H, 5·2; N, 2·3; Br, 14·8. $C_{35}H_{28}NBr$ requires C, 77·5; H, 5·2; N, 2·6; Br, 14·8 per cent), and *γ-picolinium*-2:3:4:5-*tetraphenyl*cyclo*pentadienylide*, m.p. 208–210° (89 per cent yield from (XV)) (Found: C, 90·2; H, 5·5; N, 3·0. $C_{35}H_{27}N$ requires C, 91·1; H, 5·9; N, 3·0 per cent). β- and α-Picoline, 2:6-lutidine, quinoline and *iso*quinoline were allowed to react similarly with the bromodiene, but β-picoline alone of these gave a worthwhile yield of the hydrobromide intermediate.

Acknowledgements—We thank Mr. P. R. W. Baker of the Wellcome Research Laboratories for his help in carrying out elementary analyses.

We are also indebted to the University of St. Andrews and the Department of Scientific and Industrial Research for research awards (to J. S. S.).

[23] Ng. Ph. Buu-Hoi, *Liebigs Ann.* **556**, 1 (1944).
[24] H. Kainer, *Liebigs Ann.* **578**, 232 (1952).

Tetrahedron, 1958, Vol. 3, pp. 339–352. Pergamon Press Ltd., London

STABLE π-ELECTRON SYSTEMS AND NEW AROMATIC STRUCTURES

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(*Received* 21 *January* 1958)

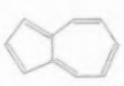
Abstract—Aromatic character, as expressed in the reactions of azulene and its derivatives, is correlated with the development, in the appropriate transition state, of a stable π-electron system (sextet) in the five- or the seven-membered ring.

The recognition that considerable stability is associated with the ions and radical derived from perinaphthene leads to the formulation of several new types of hydrocarbons which may be expected to show aromatic character. A brief theoretical consideration of these hydrocarbons is given.

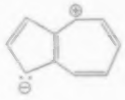
The synthesis of carbocyclic and heterocyclic derivatives of one of these hydrocarbons, *cyclo*penta[*a*]perinaphthene, is outlined, and a detailed account of their properties is given.

ASIDE from the benzenoid hydrocarbons, azulene and its derivatives constitute the only recognised class of condensed and fully conjugated cyclic hydrocarbons that show pronounced aromatic character. Although azulene is capable of representation

I (a)



I (b)



I (c)

II

III

as a hybrid of two equivalent, neutral and covalent forms, (Ia) and (Ib), aromatic character in this hydrocarbon has been correlated with effective contribution of dipolar structures, such as (Ic), to the description of the molecule in its reacting form[1] and in the ground state.[2] The implied polarisation of the molecule is considered to be the condition set by two opposing tendencies. The whole assemblage of π-electrons tends to partition itself into two stable π-electron systems (sextets) such that the five-membered ring should assume the form of the *cyclo*pentadienide anion (II), and the seven-membered ring that of the *cyclo*heptatrienylium cation (III). This is opposed by electrostatic forces that work towards the mutual annihilation of charges of opposite sign developed in the polarisation. The observed dipole moment[3] of azulene serves as the best evidence that the molecule is polarised in the ground state, but the low value of the moment ($\mu = 1{\cdot}0$ Debye) emphasises that dipolar forms, e.g. (Ic), contribute to a small extent only. The behaviour of azulene in reactions considered expressive of aromatic character indicates that it is during reaction that importance

[1] A. G. Anderson, Jr., J. A. Nelson and J. T. Tazuma, *J. Amer. Chem. Soc.* **75**, 4980 (1953).
[2] W. H. Stafford and D. H. Reid, *Chem. & Ind.* 277 (1954).
[3] G. W. Wheland and D. E. Mann, *J. Chem. Phys.* **17**, 264 (1949).

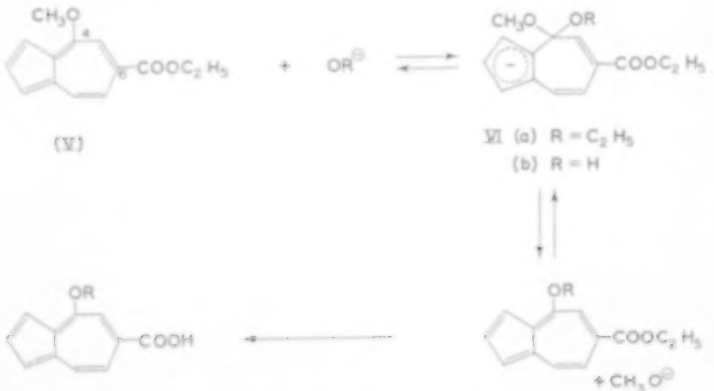
must be attached to the stability of π-electron sextets associated with the five- and seven-membered rings. In general, if attack at a site in one ring is accompanied by the development of a π-electron sextet in the other, the transition-state energy will be favourably low and reaction will be facilitated.

In substitution by an electrophilic reagent $R^{\oplus}$, a process known[1] to occur at (C_1), the transition state may be represented by the Wheland type of structure (IV) in which a sextet of π-electrons becomes associated with the now positively charged seven-membered ring.

(IV)

The characteristically high basicity of azulene is due to the stability of this type of transition state, here the azulenium ion[4] itself (IV, R = H), which results from an electrophilic attack in which the acid transfers a proton to (C_1) of the hydrocarbon base.

It has also been shown that nucleophilic replacement of substituents in the seven-membered ring of azulene may proceed under mild conditions. The ester obtained,[5] *inter alia*, by the action of ethyl diazoacetate on 4-methoxyindane, and considered on spectroscopic grounds to be 4-methoxyazulene-6-carboxylic acid ethyl ester (V), suffers ready replacement of the methoxy group when solvolysed by boiling ethanolic or aqueous potassium hydroxide to give, respectively, 4-ethoxy- and 4-hydroxy-azulene-6-carboxylic acid (VIIa and VIIb). These observations are rationalised by the following reaction scheme:



(V)

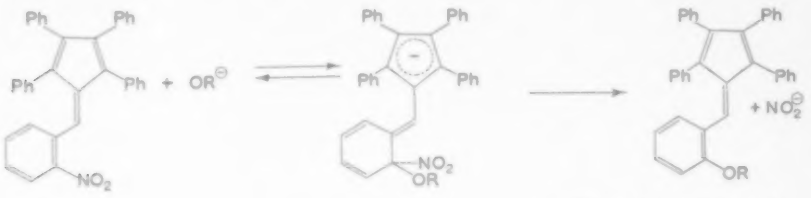
VI (a) R = C_2H_5
(b) R = H

VII (a) R = C_2H_5
(b) R = H

Nucleophilic attack at the effective site, (C_4), leading to the transition intermediate (VIa, R = C_2H_5; VIb, R = H), is rendered facile through delocalisation of the introduced negative charge by (*i*) the ester group attached to (C_6) and (*ii*) the formation of a π-electron sextet in the five-membered ring.

[4] E. Heilbronner and M. Simonetta, *Helv. Chim. Acta* **35**, 1049 (1952).
[5] D. H. Reid, W. H. Stafford and J. P. Ward, *J. Chem. Soc.* 1100 (1958).

The view that the development of a π-electron sextet in the five-membered ring plays an important part in creating readily an electron-deficient centre at the point of attack (C_4) receives independent support from the observation that 1-*o*-nitrobenzylidene-2:3:4:5-tetraphenyl*cyclo*pentadiene (VIII) is converted to 1-*o*-alkoxybenzylidene-2:3:4:5-tetraphenyl*cyclo*pentadiene (IX, R = CH_3 or C_2H_5) by the action of a boiling solution of potassium alkoxide in the appropriate alcohol. The following representation is in accord with these observations:



(VIII) (IX, R=CH_3 or C_2H_5)

The common feature of the reactions considered is the assistance given to the nucleophilic substitution process by the formation of a π-electron sextet in the five-membered ring; this stabilises the negative charge introduced by the attacking reagent.

Aromatic character is therefore associated with stable π-electron systems that either exist already in the ground state, as in the benzenoid hydrocarbons, or are capable of development during reaction, as in the azulenes. In the aromatic hydrocarbons hitherto studied a single π-electron system, the π-electron sextet, has served in the interpretation of the chemistry of these compounds.

The possibility that other stable mobile-electron systems may be capable of existence has led us to prepare and study new classes of aromatic hydrocarbons in which positively and negatively charged structures other than simple five-, six- and seven-membered rings would serve as frameworks for the delocalisation of stable

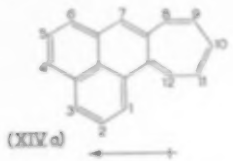
(X) (XI) (XII) (XIII)

π-electron systems. In particular, it appeared that the perinaphthene nucleus might serve satisfactorily in both capacities, as judged from a study of the properties of compounds containing this nucleus. An important feature of the chemistry of such compounds is the tendency for the three six-membered rings to function as a structural unit in which a stable system of (fourteen, thirteen or twelve) π-electrons is developed during reaction. Perinaphthene (X) is acidic,[6] and when treated with strong bases, e.g. $CH_3O^{\ominus}$ and $C_6H_5^{\ominus}$, forms the red perinaphthenide anion (XI) in which fourteen π-electrons are delocalised over the tricyclic framework of thirteen carbon nuclei.

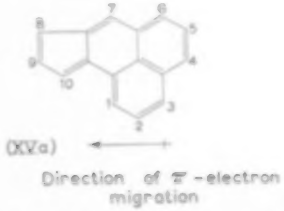
The modified carbonyl properties of perinaphthenone (XII) suggest that the perinaphthene nucleus may also give rise to a stable cation when associated with the

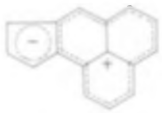
[6] V. Boekelheide and C. E. Larrabee, *J. Amer. Chem. Soc.* **72**, 1245 (1950).

appropriate number of π-electrons. Perinaphthenone is unusually highly basic,[7] dissolving reversibly in concentrated hydrochloric acid, and the CO stretching frequency in the infra-red spectrum[8] is abnormally low (1637 cm^{-1}). These properties, reflecting an unusually high polarisation of the carbonyl group, imply that considerable stability must be attributed to the perinaphthenylium cation (XIII) in which twelve π-electrons are delocalised over the perinaphthene nucleus. The preparation in this laboratory of several compounds believed to contain the cation (XIII)[9] will be described below. As a result of the recognition of these stable structures (XI) and (XIII), several new types of potentially aromatic hydrocarbons may be arrived at theoretically, and these are as follows.



(*i*) cyclo*Hepta*[a]*perinaphthene*. Fusion of the perinaphthene nucleus to a seven-membered ring gives the skeleton of *cyclo*hepta[*a*]perinaphthene (XIVa). In the completely polarised form of the hydrocarbon fourteen π-electrons are delocalised over the perinaphthene nucleus and a sextet of π-electrons is associated with the seven-membered ring. This limiting structure (XIVb) reflects the sense of the expected polarisation. It may be predicted that electrophilic attack will occur readily at one or more of the chemically recognisable positions (C_1, C_3, C_4, C_6 and C_7) on the periphery of the perinaphthene nucleus, and that the expected high basicity will be associated with the same position(s).



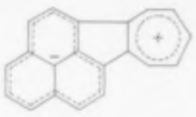


(*ii*) cyclo*Penta*[a]*perinaphthene*. The hydrocarbon (XVa) results from fusion of a five-membered ring to the perinaphthene nucleus. In the completely polarised structure (XVb) a sextet of π-electrons is associated with the five-membered ring, which takes the form of the *cyclo*pentadienide anion (II), while the perinaphthene skeleton, embracing twelve π-electrons, assumes the form of the perinaphthenylium cation (XIII). Electrophilic attack is expected to take place at (C_{10}) or (C_8) or both, the positions at which proton uptake in acid media should occur most readily. The synthesis and study of several hydrocarbon and heterocyclic derivatives of *cyclo*-penta[*a*]perinaphthene is described below.

[7] E. Bamberger and M. Philip, *Liebigs Ann.* **240**, 178 (1887); J. W. Cook and C. L. Hewett, *J. Chem. Soc.* 365 (1934).
[8] N. H. Cromwell and G. V. Hudson, *J. Amer. Chem. Soc.* **75**, 872 (1953).
[9] D. H. Reid, *Angew. Chem.* 761 (1955); I. M. Aitken and D. H. Reid, *J. Chem. Soc.* 3487 (1956).

Owing to the re-entrant form of the periphery of the perinaphthene skeleton, a further two types of dipolar aromatic hydrocarbons are possible. These are *cyclo*hepta[*cd*]perinaphthene (XVIa) and *cyclo*penta[*cd*]perinaphthene (XVIIa), resulting from a new mode of union of the seven- and the five-membered rings, respectively, with the perinaphthene nucleus.

(XVI a)



(XVI b)

(*iii*) cyclo*Hepta*[cd]*perinaphthene*. A new structural feature is the formal independence of the π-electron systems in the completely polarised form (XVIb). In this respect *cyclo*hepta[*cd*]perinaphthene differs from the dipolar hydrocarbons previously considered, viz., azulene (I), *cyclo*hepta[*a*]perinaphthene (XIV) and *cyclo*penta[*a*]perinaphthene (XV), in the the completely polarised forms of which a pair of π-electrons is common to both stable π-electrons systems. As in the case of *cyclo*hepta[*a*]perinaphthene, anionic reactivity, including basicity, is expected to be shown by the perinaphthene moiety.

(XVII a)

(XVII b)

(*iv*) cyclo*Penta*[cd]*perinaphthene*. *cyclo*Penta[*cd*]perinaphthene (XVIIa and completely polarised form XVIIb) may be similarly derived by union of a five-membered ring at adjacent positions, with the perinaphthene nucleus at a pair of peri-carbon atoms. Since a five-membered ring shows ionic stability only when associated with a sextet of π-electrons, anionic character and basicity will be shown by the five-membered ring in (XVIIa).

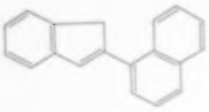
EXPERIMENTAL RESULTS

Indeno[2,1-a]*perinaphthene*[9] (XX)

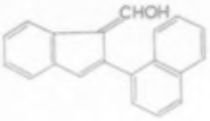
Two positions (C_8 and C_{10}) in the five-membered ring of *cyclo*penta[*a*]perinaphthene (XV) are expected to show nucleophilic reactivity, but they are not equivalent. Indeno[2,1-*a*]perinaphthene (XX), a ring homologue of (XV), possesses one chemically recognisable position in the five-membered ring, and a study of this hydrocarbon was undertaken first.

Synthesis. The reaction of indan-2-one and 1-naphthylmagnesium bromide followed by dehydration of the crude product gave 1-2′-indenylnaphthalene (XVIII), m.p. 90–91°. Condensation of this hydrocarbon with ethyl formate in the presence of potassium methoxide afforded the unstable hydroxymethylene derivative (XIX), which, when treated with 93% sulphuric acid, underwent peri-cyclisation to give indeno[2,1-*a*]perinaphthene (XX) as reddish-brown leaflets, m.p. 210–211°. A second, purple-black, hydrocarbon, m.p. 294–297°, was formed concomitantly in smaller amount. It has been shown to contain two nuclei of indeno[2,1-*a*]perinaphthene and probably possesses structure (XXI).

Basicity. The most characteristic property of indeno[2,1-*a*]perinaphthene is its high basicity. The hydrocarbon dissolves reversibly in strong acids, e.g., in 72% perchloric acid and 65% sulphuric acid, to form a green cation. A measure of the

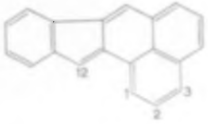


(XVIII)



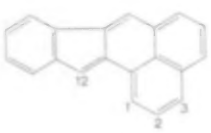
(XIX)

(XXI)

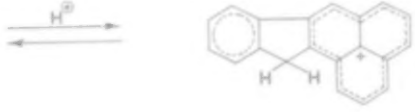


(XX)

basicity was obtained by the procedure of Plattner *et al.*,[10] by which the hydrocarbon was partitioned between *cyclo*hexane and sulphuric acids of different strengths. A linear relation was found to exist between $\log_{10} K'$ (where K' is the apparent partition coefficient) and the Hammett acidity function H_0, and the slope of the straight line was found to approximate closely to two.[11] The H_0 value found (−4·80) for which K' is unity corresponds to an acid concentration of 64% w/w sulphuric acid; this value places indeno[2,1-*a*]perinaphthene alongside the azulenes in order of basicity.[12] In the light of the reasoning outlined above the conjugate acid is considered to possess structure (XXII), resulting from accession of a proton to (C_{12}). Addition of a proton at this position is accompanied by formation, in the perinaphthene nucleus, of the π-electron system present in the perinaphthenylium cation (XIII).



(XX)



(XXII)

Electrophilic substitution. Substitution occurs readily under mild conditions. The position involved has not yet been determined experimentally, but is held to be the 12-position.

A violet mononitroindeno[2,1-*a*]perinaphthene (XXIIIa), m.p. 186–190° (dec.), is formed at room temperature when (XX) in pyridine–ethanol solution is treated with tetranitromethane. The abnormally low value (1506 cm^{-1}) of the nitro group anti-symmetrical N—O stretching frequency* in the infra-red spectrum is consistent with the view that the nitro group occupies the 12-position, structure (XXIIIb) contributing appreciably to the resonance hybrid.

* An average value given for this vibration is 1518 cm^{-1} (see Randle and Whiffen[13]).

[10] P. A. Plattner, E. Heilbronner and S. Weber, *Helv. Chim. Acta* **32**, 574 (1949).

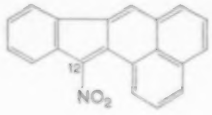
[11] V. Gold and F. L. Tye, *J. Chem. Soc.* 2181 (1952).

[12] D. H. Reid, W. H. Stafford and J. P. Ward, *J. Chem. Soc.* 1193 (1955).

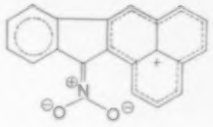
[13] R. R. Randle and D. H. Whiffen, *J. Chem. Soc.* 4153 (1952).

Acylation may be effected by reactive acid halides without the aid of catalysts normally required in reactions of the Friedel–Crafts type. By using acetyl bromide as the reagent a monoacetylindeno[2,1-*a*]perinaphthene was formed.

The course of halogenation is less well defined. Passage of bromine vapour in a stream of nitrogen into a solution of (XX) in carbon tetrachloride at room tempera-



(XXIII a)



(XXIII b)

ture gave a mixture of monobromoindeno[2,1-*a*]perinaphthenes, one of which, however, constituted upwards of 95 per cent of the product. It has been established that the predominating isomer is either 1-bromoindeno[2,1-*a*]perinaphthene or 12-bromoindeno[2,1-*a*]perinaphthene, since bromine was lost and the anhydride (XXV) was formed in a Diels–Alder reaction (see next section) with maleic anhydride in nitrobenzene. On theoretical grounds the latter alternative structure is preferred.

XXIV XXV XXVI

XXIX XXVIII XXVII

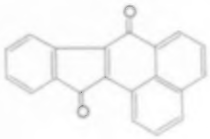
Diene reactivity. Indeno[2,1-*a*]perinaphthene functions readily as the diene in Diels–Alder reactions. Addition has been shown to involve the 1- and the 12-positions. Thus, with maleic anhydride in boiling xylene–acetic acid, it gives a colourless adduct (XXIV). This adduct was dehydrogenated by boiling nitrobenzene, and the resulting fully aromatic anhydride (XXV) was decarboxylated to the yellow hydrocarbon indeno[1,2,3-*cd*]pyrene (XXVI), m.p. 161·5–163°, whose structure was established with the aid of an independent synthesis. A crossed Ullmann reaction between 1-iodopyrene and *o*-bromonitrobenzene gave 1-*o*-nitrophenylpyrene (XXVII), which, by successive reduction to the corresponding amine, diazotisation and treatment with copper bronze, was converted into the same hydrocarbon (XXVI). The synthesis of indeno[1,2,3-*cd*]pyrene from 1-(1-hydroxymethylene-2-indenyl)naphthalene (XIX)

and from 1-*o*-nitrophenylpyrene (XXVII) served to establish the constitution of both (XX) and (XXVI).

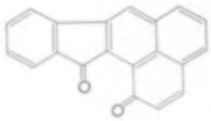
Other dienophiles that form adducts with (XX) include 1:4-benzoquinone, 1:4-naphthaquinone and 7-bromoacenaphthylene. The reaction of the last-mentioned compound with indeno[2,1-*a*]perinaphthene in nitrobenzene to form (XXVIII) represents the first recorded instance in which 7-bromoacenaphthylene has served as a dienophile.

The very ready reactions of indeno[2,1-*a*]perinaphthene with dienophiles reflects the ease with which a pair of π-electrons may be localised at (C_1) and (C_{12}). It is suggested that, in accord with Robinson's views[14] on the mechanism of the Diels–Alder reaction, structure (XXIX) contributes significantly to the electronic description of the transition state.

Oxidation. With chromic anhydride in acetic acid as the oxidising agent, quinone formation takes place. The resulting orange-red quinone, m.p. 290–292°, which gives a violet-blue vat with alkaline dithionite, possesses structure (XXX) or (XXXI). The



(XXX)



(XXXI)

infra-red spectrum is consistent with either structure. Two prominent bands occur in the CO region. One of these, occurring at 1704 cm^{-1}, is close to that of fluorenone[15] (1715 cm^{-1}). The other band appears at 1639 cm^{-1}, thus falling in the region in which perinaphthenones absorb characteristically.*

Reduction. Chemical reduction of indeno[2,1-*a*]perinaphthene by zinc in acetic acid yielded a homogeneous dihydroindeno[2,1-*a*]perinaphthene, m.p. 169·5–171·5°. Further reduction by catalytic hydrogenation (platinic oxide in acetic acid) afforded a colourless tetrahydroindeno[2,1-*a*]perinaphthene which must possess structure (XXXII) or (XXXIII), since its ultra-violet spectrum resembles closely the ultra-violet spectra of 1:2- and 2:3-benzofluorene. If the possibility is precluded that the dihydro-

(XXXII)

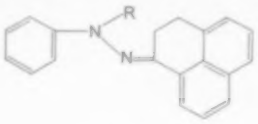
(XXXIII)

indeno[2,1-*a*]perinaphthene underwent rearrangement under the conditions of the catalytic reduction, it follows that in the course of chemical reduction indeno[2,1-*a*]-perinaphthene adds on one hydrogen atom at (C_{12}) and a second at one of the positions (C_1), (C_3), (C_4) and (C_6). Four structures are therefore possible for the dihydroindeno[2,1-*a*]perinaphthene.

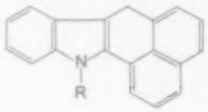
* See ν_{CO} for (XII),[8] (XLII) or (XLIII) and (XLVI).

[14] B. J. F. Hudson and R. Robinson, *J. Chem. Soc.* 715 (1941).
[15] E. D. Bergmann, G. Berthier, D. Ginsburg, Y. Hirschberg, D. Lavie, S. Pinchas, B. Pullman and Pullman, *Bull. Soc. Chim. Fr.* **18**, 661 (1951).

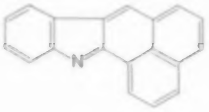
The dihydroindeno[2,1-*a*]perinaphthene undergoes with striking readiness two aromatisation reactions, which reflect the aromatic character of indeno[2,1-*a*]perinaphthene. When a solution of the dihydro derivative in benzene containing pyridine is treated at room temperature with osmium tetroxide, indeno[2,1-*a*]perinaphthene is obtained in fair yield. The parent hydrocarbon is also re-formed when a solution of the dihydroindeno[2,1-*a*]perinaphthene in acetic acid is allowed to stand at room



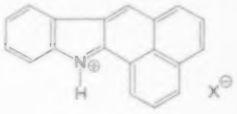
(XXXIV)



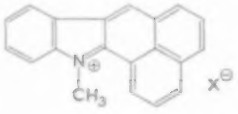
(XXXV)



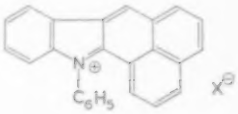
(XXXVI)



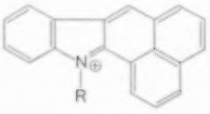
(XXXVII)



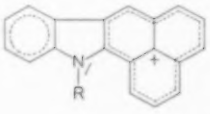
(XXXVIII)



(XXXIX)



(XL a)



(XL b)

temperature in the presence of 20% palladised charcoal. In boiling solution dehydrogenation is completed in a few minutes.

Heterocyclic derivatives. The phenylhydrazone (XXXIV, R = H) of perinaphthan-1-one, on being boiled for a short time in acetic acid, is converted into the indole (XXXV, R = H) in low yield. Conversion of (XXXV, R = H) to the fully aromatic base, indolo[2,3,-*a*]perinaphthene (XXXVI), could not be effected by standard dehydrogenation procedures. However, an almost quantitative yield of the hydriodide (XXXVII, X = I) of indolo[2,3-*a*]perinaphthene was obtained by the

action of iodine on a boiling solution of (XXXV, R = H) in methanol or acetone. The base (XXXVI) itself is unstable and its orange-red solutions in organic solvents yield an intractable residue on evaporation of the solvent. This accounts for the previously encountered failure to prepare (XXXVI).

Other derivatives, e.g. the picrate (XXXVII, X = picrate) and the perchlorate (XXXVII, X = ClO_4), have been prepared by the action of the corresponding acids on a solution of the hydriodide in methanol. These salts decompose at somewhat elevated temperature without showing definite melting points, and dissolve only in polar solvents, preferably methanol, to give crimson solutions.

In a similar series of reactions the N-methylphenylhydrazone (XXXIV, R = CH_3) was converted into the indole (XXXV, R = CH_3) and thence into the methiodide (XXXVIII, X = I) and the methoperchlorate (XXXVIII, X = ClO_4) of indolo [2,3-*a*]perinaphthene. A superior method for the preparation of (XXXVII, X = ClO_4) and (XXXVIII, X = ClO_4) consists in boiling a solution of the indole (XXXV, R = H or CH_3) in acetic acid containing an excess of 72% $HClO_4$, when the salt is formed directly. The dehydrogenation of these indoles proceeds in the absence of oxygen and requires the presence of a strong acid.

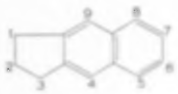
The preparation of the perchlorate (XXXVII, X = ClO_4), the methoperchlorate (XXXVIII, X = ClO_4), and the N-phenylperchlorate (XXXIX) of indolo[2,3-*a*]perinaphthene may be telescoped into a one-step reaction by boiling a solution of perinaphthan-1-one in acetic acid containing phenylhydrazine or the appropriately substituted phenylhydrazine and an excess of 72% perchloric acid.

Undoubtedly the indolo[2,3-*a*]perinaphthenylium structure (XLb, R = H, CH_3 or C_6H_5) makes significant contribution to the resonance hybrid of the cation (XLa, R = H, CH_3 or C_6H_5).

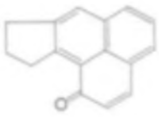
cyclo*Penta*[a]*perinaphthene* (XV)

Preliminary studies on *cyclo*penta[*a*]perinaphthene have been confined to attempts to synthesise compounds containing the carbon skeleton of the hydrocarbon.

In one approach acetylation of 2:3-*cyclo*pentenonaphthalene (XLI)[16] with acetyl chloride and aluminium chloride in 1:2-dichloroethane gave a mixture in which the



(XLI)

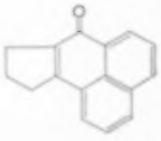


(XLII)

(XLIII)

(XLIV)

(XLV)



(XLVI)

[16] F. J. McQuillin and R. Robinson, *J. Chem. Soc.* 586 (1941).

presence of two monoacetyl-2:3-*cyclo*pentenonaphthalenes was detected. The predominating isomer was condensed with ethyl formate in the presence of potassium methoxide, and the resulting hydroxymethylene derivative, on cyclisation with 87% sulphuric acid, formed a yellow ketone, m.p. 81–82°. This was reversibly soluble in concentrated hydrochloric acid and showed infra-red carbonyl absorption at 1637 cm^{-1}. The cyclisation product is therefore 8:9-*cyclo*pentenoperinaphthenone (XLII) or 4:5-*cyclo*pentenoperinaphthenone (XLIII), and the monoacetyl-2:3-*cyclo*pentenonaphthalene is, correspondingly, the 4- or the 5-isomer. The isomer isolated in low yield (about 7 per cent) from the acetylation of (XLI) is 6-acetyl-2:3-*cyclo*pentenonaphthalene.

Elimination of oxygen from the *cyclo*pentenoperinaphthenone (XLII) or (XLIII) by the use of lithium aluminium hydride[17,6] afforded in high yield a *cyclo*pentenoperinaphthene, to which structure (XLIV) is arbitrarily assigned. Attempts to dehydrogenate this hydrocarbon to *cyclo*penta[*a*]perinaphthene, catalytically, under a variety of conditions, or, chemically, by heating with sulphur, gave no useful product. When bromination with N-bromosuccinimide was carried out as the initial step in an attempted bromination–dehydrobromination procedure, formation of the transient *cyclo*pentenoperinaphthyl radical (XLV) ensued. This radical subsequently formed a high-melting solid, probably a di*cyclo*pentenoperopyrene (cf. the formation of peropyrene from perinaphthyl).

A second possible route to (XV) that is being currently investigated is based on the observation that 2:3-*cyclo*pentenoperinaphthenone (XLVI), m.p. 147–148° (infra-red CO absorption at 1634 cm^{-1}), is formed in substantial yield when naphthalene is treated with *cyclo*pentene-2-carboxylic acid chloride in the presence of an excess (3 moles) of aluminium chloride.

Perinaphthyl radicals[18]

Synthesis of perinaphthyl. A consideration of the symmetry of the carbon sleketon in perinaphthene (X) has led to the suggestion[6,19,20] that perinaphthyl (XLVII) may be a stable long-lived radical. Four oxygenated derivatives of perinaphthyl have already been reported. One of these, 1-hydroxy-3-phenylperinaphthyl,[20] was isolated as a red solid possessing a definite melting point. The remaining three, 1-methoxyperinaphthyl, 1-acetoxyperinaphthyl and 1-benzoyloxyperinaphthyl, were observed[19] as their blue solutions. Several attempts[6,20] to prepare the parent radical (XLVII) were unsuccessful.

We have observed the formation of this entity in five distinct reactions:

(*i*) In the best method for the preparation of perinaphthyl, the perinaphthenide anion (XI), prepared from perinaphthene and potassium methoxide in a 2% ethanolic ether solution, was shaken at room temperature in the presence of oxygen. Perinaphthyl arose in the process by a spontaneous one-electron transfer from the anion (XI) to molecular oxygen, which was thereby converted to the peroxide anion.

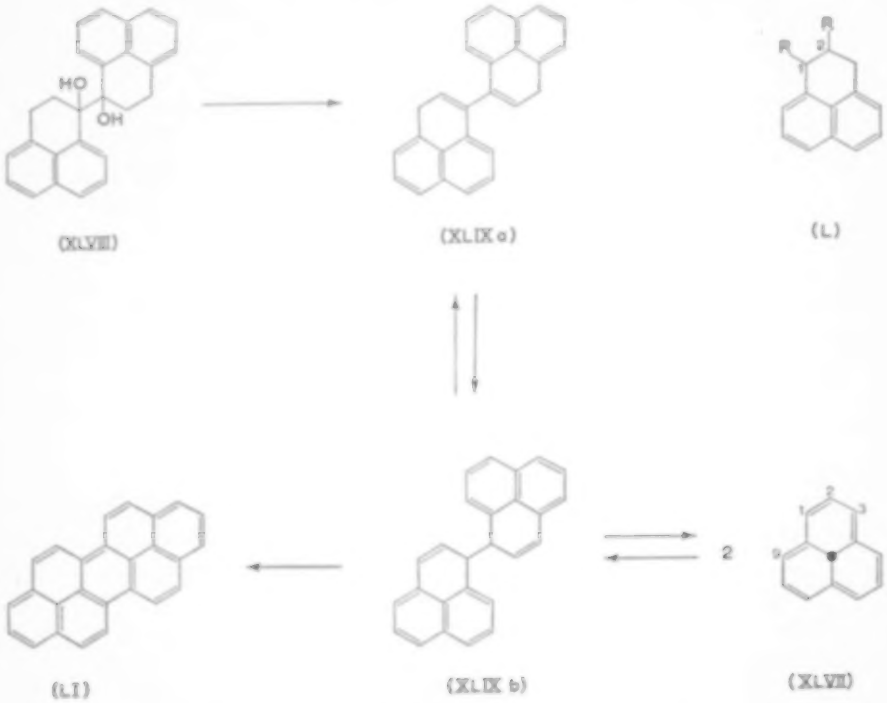
(*ii*) A second method, of theoretical significance, started with the diol (XLVIII), which was obtained as the bimolecular reduction product from perinaphthan-1-one and amalgamated aluminium in ethanol–benzene. The addition of a catalytic

[17] F. A. Hochstein, *J. Amer. Chem. Soc.* **71**, 305 (1949).
[18] D. H. Reid, *Chem. & Ind.* 1504 (1956).
[19] E. Clar, *Aromatische Kohlenwasserstoffe* (2nd Ed.) p. 431. Springer Verlag, Berlin (1952).
[20] V. Boekelheide and M. Goldman, *J. Amer. Chem. Soc.* **76**, 604 (1954).
[21] C. F. Koelsch and J. A. Anthes, *J. Org. Chem.* **6**, 558 (1941).

(XI) (XLVII)

amount of concentrated hydrochloric acid to a solution of the diol (XLVIII) in propionic acid at room temperature resulted in immediate formation of the blue perinaphthyl (XLVII).

Under the prevailing conditions acid-acatalysed prototropy involving the intermediately formed dehydration product (XLIXa) gives rise to isomer (XLIXb), the



(XLVIII) (XLIX a) (L)

(LI) (XLIX b) (XLVII)

dimeric form of perinaphthyl. Subsequent spontaneous fission of the C–C bond joining the perinaphthene moieties in (XLIXb) affords the radical (XLVII).

(*iii*) Treatment of 1:2-dibromoperinaphthane (L, R = Br) with organic bases resulted in the loss of hydrogen bromide and bromine and formation of (XLVII) (see Boekelheide and Larrabee[6]).

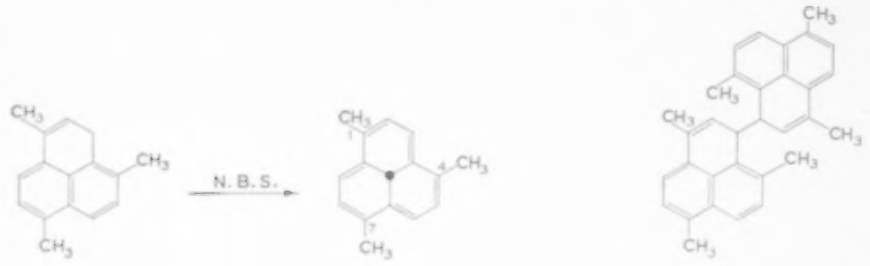
(*iv*) Perinaphthyl also results when perinaphthene is treated with N-bromosuccinimide (see Boekelheide and Larrabee[6]). This procedure assumed importance in the preparation of the substituted perinaphthyls (XLV) and (LIII).

(*v*) Finally, perinaphthyl was formed along with the normal product *cis*-1:2-dihydroxyperinaphthane (L, R = OH), m.p. 142–144°, when perinaphthene was allowed to react with osmium tetroxide and pyridine in benzene solution.

Properties of perinaphthyl. Perinaphthyl is green in the solid state, but has not in this form been isolated pure. It fails to react with nitric oxide. With oxygen it readily affords a green peroxide, $C_{26}H_{18}O_2$, which possesses no definite melting-point and breaks down on being heated *in vacuo* into a mixture of peropyrene (LI) and perinaphthenone (XII). The structure of this somewhat unstable compound is uncertain.

From a consideration of the first two methods of preparation of (XLVII) it follows that an equilibrium between perinaphthyl and its dimeric form is theoretically possible. It has been found, however, that the dimeric form disproportionates into peropyrene (LI) and a hitherto unidentified hydroaromatic product. This irreversible process takes place slowly at room temperature, but it is completed in seconds when the solvent is (benzene or acetic acid) at its boiling point. The thermal instability of the dimeric form of perinaphthyl thus accounts for the earlier failures to prepare this radical.

1:4-7-*Trimethylperinaphthyl* (LIII). The formation of a molecule of peropyrene in the disproportionation process involves the eventual linking of two perinaphthyl radicals, each through a pair of peri-positions (C_1 and C_9). A derivative, 1:4:7-trimethylperinaphthyl (LIII), was therefore synthesised in which one position of each of the three pairs of peri-positions is substituted by a methyl group. Aromatisation of the dimeric form (LIV) is thus impossible. In agreement with expectation the violet-blue radical (LIII) was found to be stable in the absence of oxygen at 240°. It is



LII LIII LIV

noteworthy that 1:4:7-trimethylperinaphthyl could not be prepared by the action of oxygen on a solution of (LII) in ethanolic ether containing potassium methoxide. The presence of the three methyl substituents in (LII) suppresses the ionisation of the hydrocarbon to a degree at which, under the reaction conditions, the equilibrium concentration of the corresponding anion is inadequately low.

The perinaphthenylium cation (XIII). The possibility of completing the sequence:

perinaphthene → perinaphthenide → perinaphthyl → perinaphthenylium

has been realised in the successful conversion of perinaphthyl to perinaphthenylium salts. The halogens chlorine, bromine and iodine all react with the radical to form products whose stabilities follow the order iodide > bromide > chloride. The iodide ($C_{13}H_9I$) is indefinitely stable when stored under nitrogen. The bromide is much less stable and slowly evolves hydrogen bromide, passing over to peropyrene (LI) and a bromine-containing contaminant. The chloride has not been isolated as a solid. Studies in this series have been confined mainly to the iodide. This compound,

as isolated by the action of iodine on an ethereal solution of perinaphthyl, is a violet-black solid possessing no definite melting point but decomposing to an orange-yellow solid on being heated. It is insoluble in most organic solvents; it dissolves to a small extent only in nitromethane (green solution), but very readily in pyridine and related bases to form greenish-blue solutions. These solutions contain the perinaphthyl radical, which may be recovered by addition of water and then extraction with ether. In boiling pyridine the iodide is rapidly transformed into peropyrene (LI).

(LV)

(LVI)

(LVII)

(LVIII)

The properties of the iodide (LV, X = I) are consistent with the view that in the solid state the bond between iodine and the organic moiety is largely ionic in character, but that the molecule breaks down homolytically in pyridine to form the radical (XLVII). It is significant that pyridine forms a molecular complex with the iodine molecule,[22] a process that would assist the homolytic cleavage. A marked increase in the stability of the coloured entity is observed when the iodide is added to nitromethane containing a Lewis acid, e.g. aluminium chloride or stannic chloride. The resulting deep-green solutions are stable at the boiling point.

Conversion of the perinaphthyl radical to the perinaphthenylium cation has also been achieved by using as electron acceptor a metallic ion possessing a ready tendency to assume the metallic state. Thus perinaphthyl and anhydrous silver perchlorate react in ether solution to form perinaphthenylium perchlorate (LV, X = ClO_4) and metallic silver. This salt is readily soluble in nitromethane to give yellowish-green solutions, from which it is precipitated as a black solid on the addition of ether. It shows no definite melting point, but it decomposes slowly on being heated and readily undergoes hydrolysis.

The perinaphthenylium cation (XIII) and heptalene (LVI) are isoelectronic with the unknown polyolefin *cyclo*duodecahexaene (LVII), which, however, cannot be planer owing to "H–inside" steric compression. In order to examine further the stability of such peripheral conjugated systems of π-electrons attempts are being made to replace the formally positively charged central carbon atom of (XIII) by tervalent elements, in particular boron. In the resultant neutral molecule (LVIII, R = B) the central hetero-atom serves to hold the peripheral structure in a planar configuration free of "angle" strain.

[22] L. F. Audrieth and E. J. Birr, *J. Amer. Chem. Soc.* **55**, 668 (1933).

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BOND CHARACTER, BOND ORDER AND THE QUADRIVALENCY OF CARBON

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Abstract—When the chemical bond is treated as a resultant without specific reference to its exact nature, a consistent interpretation of the relationship between the various types of carbon–carbon bonds is possible. The terms bond character, bond order and quadrivalency are considered in the light of this interpretation. It is emphasised that the chemical bond must be regarded as a vector quantity involving both direction and magnitude factors.

THE idea of the chemical bond lies at the root of our knowledge of the structure of molecules and without it the science of organic chemistry could hardly have developed. Saturation and unsaturation, the tetrahedral disposition of the bonds of carbon and many other accepted principles of molecular structure are all developments from the primitive bond theory. It was inevitable, when something was learnt about the inner structure of atoms, that the electronic nature of chemical bonds should be discovered and the stage set for more detailed investigations into their exact make-up. A host of physical and mathematical methods and many interpretations of the results obtained have been brought to bear on the problem. The consequent, rapidly advancing branch of knowledge consists of established facts, constantly changing techniques and numerous exploratory theories all inter-connected in an increasingly complex pattern.

What will be said here deals with a small chapter of this large and expanding science and uses as its basis the measurements of bond lengths, bond angles and bond energies recorded in the literature. An attempt is made to rationalise the relation between the old and the new points of view on chemical binding and molecular structure. There is no intention of trying to make a critical review of the present state of knowledge, even in a restricted field.

Whatever else the old-fashioned chemical bond may be, it must be regarded as a resultant of many contributing factors concerned with nuclear and electronic attractions, repulsions and movements. It is represented as a straight line joining what are considered to be the mean positions of the nuclei of the atoms linked by it. It is, therefore to be characterised by its length (i.e. the internuclear distance) and its direction. The length is a function of the bond energy, but it must be pointed out that scientists are not unanimous as to what the term bond energy means. In this discussion the values worked out by Pauling[1] and called by him "empirical" will be used.

There is another fundamental matter involved, namely, the quadrivalency of carbon. It may seem obvious that, taking hydrogen as univalent and knowing that methane has the composition CH_4, the valency of carbon must necessarily be four.

[1] L. Pauling, *Nature of the Chemical Bond* (2nd Ed.) pp. 53 and 131. Cornell University Press, New York (1945).

The simple addition, however, of four univalent bonds to make a total valency of four leaves out of consideration the directions of the bonds and this omission, as we shall see later, may give rise to misleading conclusions.

The particular aspect of "bond science" to be dealt with first is the classification of bonds according to "character" or "order". This assumes considerable importance in connection with the C,C bonds in benzene, graphite and conjugated systems.

When the symmetry of the benzene ring, its planarity and the equality in length of its C,C bonds are considered in the light of the older ideas of valency, it is natural to conclude that the bonds are half-way between double and single bonds in "character." Pauling and Brockway[2] used this terminology in discussions on the presumed resonance of benzene and allied structures. Their equation

$$d = 1{\cdot}54 - 0{\cdot}20[3x/(2x + 1)]$$

connects double-bond character x with observed bond length d. It is the algebraic expression of a graph obtained by plotting four assumed bond characters (0 for a single bond, 1/3 for a graphite bond, 1/2 for a benzene bond and 1 for a double bond) against the corresponding observed bond lengths. Two things about this equation must be noticed: (*a*) it depends mainly on the two characters assumed for the C,C bonds in benzene and graphite, and (*b*) it has no reference to the triple bond. It implies that each carbon in benzene can be regarded as having a single bond linking it with hydrogen and two "one-and-a-half" bonds linking it with neighbouring carbons. The simple addition of these values to make a total of four satisfies the classical requirement of the quadrivalency of carbon.

A different approach to the quantitative definition of a chemical bond can be made by assuming that the "orders" of the bonds usually classified as single, double and triple are actually 1, 2 and 3, respectively. It is then possible to evolve an equation connecting observed bond lengths with these "orders" and at the same time to provide a means of assigning an "order" to any bond whose observed length diverges from those accepted as normal for single, double and triple bonds. From time to time many such equations have been put forward. That particularly considered here depends on the fact that the inverse squares of the bond lengths of single, double and triple C,C bonds form, within a reasonable margin of error, an arithmetic series. On this basis, Gordy[3] framed the equation $N = aR_x^{-2} - b$, in which R_x is the observed length of the bond and N its order, a and b being constants. With a suitable selection of constants, this equation is widely applicable. A better version of it, especially for C,C bonds, is:

$$N = (R_x^{-2} - k)/(R_1^{-2} - k)$$

which replaces the two constants a and b by one, k; R_1 is the length of the single bond. The numerical value of k for C,C bonds is 0·281; this is very close to the value of $\frac{2}{3}R_1^{-2}$, namely 0·279. Substituting k by $\frac{2}{3}R_1^{-2}$ and simplifying, we arrive at the expression[4] $N = (3R_1^2/R_x^2) - 2$. In this simple equation we have the means of assigning a numerical value to the order of a C,C bond of any observed length, R_x. Applying it to the benzene bonds of length 1·397 Å, we arrive at the order 1·67; for

[2] L. Pauling and L. O. Brockway, *J. Amer. Chem. Soc.* **59**, 1235 (1937).
[3] W. Gordy, *J. Chem. Phys.* **15**, 305 (1947).
[4] J. C. Earl, *Chem. & Ind.* 173 (1955).

the graphite bonds of length 1·42 Å, we get the order 1·55. These values are in surprisingly close agreement with those resulting from molecular-orbital calculations by Coulson,[5] namely, 1·67 and 1·53. It must be noted, however, that a simple summation of the orders of the bonds pertaining to any one carbon does not give a total of four. For the carbons in benzene we have 1·67 for each of the C,C bonds and 1 for the C,H bond, making a total of 4·34. In graphite, each carbon is linked to three of its neighbours by bonds of order 1·55, giving a total of 4·65. This matter will be discussed in more detail later.

At this point the question of relating bond energy to bond length must be taken up. Pauling,[1] by calculations based on the known energy changes involved in the formation of saturated hydrocarbons, assigned to the C,H bond the energy of 87·3 kcal and to the C,C bonds, 58·6 for the single bond, 100 for the double bond and 123 for the triple bond. These energy values can be correlated with the observed lengths of the bonds by plotting a curve of energy against order and working out the corresponding algebraic equation. When this is done, the equation $E = 130{\cdot}9 - 8(4 - N)^2$ is obtained.[6] The numerical value of N is available by the procedure already described; E is the bond energy. When the equation is applied to the C,C bonds of benzene, the value of 87·5 kcal is obtained for their energy.

This value of 87·5 kcal lies very close to the 87·3 kcal of the C,H bond. The agreement may be fortuitous, but it seems likely that it has important significance. There is a considerable body of evidence that the three bonds of each carbon atom in benzene are symmetrically disposed about it in one plane. In other words, their directions are at 120° to one another. If, at the same time, their energies are equal, one would expect that the arrangement would show unusual stability. A similar, symmetrical distribution of energy is involved in the structure of methane, but there it is three-dimensional as opposed to the two-dimensional distribution imposed by the planarity of the benzene molecule. A further suggestive result has been obtained by studying the distribution of energy about the carbons in the hypothetical structure for benzene containing alternate single and double bonds in the ring, commonly called the Kekulé structure, although Kekulé's original idea involved both the possible structures of this type. It is shown in a recent note[7] that the total energy involved at each carbon is the same as that in the "regular" structure, but it is unsymmetrically distributed.

One is now in a position to assign a more definite meaning to the ideas of double-bond character (p) and bond order (N). It is significant that for benzene C,C bonds the relation:

$$p = (N \cos 120^\circ / \cos 109^\circ 28') - 2$$

holds. In other words, the bond-character terminology does not take into account the divergence of the bond angles in benzene (120°) from the tetrahedral angle (109° 28′). A similar consideration has to be taken into account when looking at the apparent discrepancy between the result of the simple addition of the orders of the bonds of any carbon atom and the value of four accepted as the valency of carbon. For the carbons in benzene we have $2 \times [(1{\cdot}67 \cos 120^\circ / \cos 109^\circ 28') - 1]$ for the two C,C bonds and 1 for the C,H bond; this adds up to the required total of four. Similarly

[5] C. A. Coulson, *Proc. Roy. Soc.* A **169**, 413 (1939).
[6] J. C. Earl, *Chem. & Ind.* 1520 (1955).
[7] J. C. Earl, *Tetrahedron* **2**, 355 (1958).

for the three C,C bonds in graphite of order 1·55, we have $3 \times [(1{\cdot}55 \cos 120°/\cos 109°28') - 1] = 4$.

One conclusion to be drawn with certainty from the above discussion is that chemical bonds, i.e. the resultants of the wide variety of forces that operate in the regions between the nuclei of atoms in a molecule, must be considered always as vector quantities. They cannot be submitted to any form of quantitative calculation without taking account of both their direction and energy. Where the regular tetrahedral distribution in carbon compounds is not interfered with by ring formation or other form of restraint, the direction component may not make itself evident, but, nevertheless, it has its part.

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